STEDMAN'S
Medical Dictionary

27th Edition

Illustrated in Color

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Gestational diabetes occurs in 3–6% of all pregnancies, and although it typically resolves after delivery, as many as 60% of women with this disorder eventually develop type 2 diabetes. Diabetes occurring during pregnancy increases the risk of maternal pyelonephritis and of certain congenital anomalies, and is often associated with polyhydramnios and fetal macrosomia, with resultant dystocia. It is recommended that all pregnant women be screened for gestational diabetes between the 24th and 28th week of pregnancy by determination of the plasma glucose level 1 hour after a 50 g oral glucose load. A level above 140 mg/dL (7.8 mmol/L) is an indication for a 3-hour glucose tolerance test. Gestational diabetes can usually be managed by diet alone, but insulin is sometimes required.

growth-onset d., SYN insulin-dependent d. mellitus.

d. in'nocens, obsolete term for renal *glycosuria.*

d. insip'idus, chronic excretion of very large amounts of pale urine of low specific gravity, causing dehydration and extreme thirst; ordinarily results from inadequate output of pituitary antidiuretic hormone; the urine abnormalities may be mimicked as a result of excessive fluid intake, as in psychogenic polydipsia. Several types exist: central, neurohypophyseal, and nephrogenic. Autosomal dominant [MIM*125700, *125800, *192340], X-linked [MIM*304800 and *304900], and even autosomal recessive forms [MIM*222000] have been described. SEE ALSO nephrogenic d. insipidus.

insulin-dependent d. mellitus (IDDM), severe d. mellitus, often brittle, usually of abrupt onset during the first two decades of life but can develop at any age; characterized by polydipsia, polyuria, increased appetite, weight loss, low plasma insulin levels, and susceptibility to ketoacidosis; immune-mediated destruction of pancreatic B cells; insulin therapy and dietary regulation are necessary. Term declared obsolete by American Diabetes Association. SYN growth-onset d., juvenile-onset d., type I d.

insulinopenic d., any form of d. mellitus resulting from inadequate secretion of insulin.

d. intermit'tens, d. mellitus in which there are periods of relatively normal carbohydrate metabolism followed by relapses to the previous diabetic state.

juvenile d., d. mellitus appearing in a child or adolescent; often fatal before the discovery of insulin, usually of abrupt onset during first or second decades of life; characterized by polyuria, polydipsia, weight loss; usually severe, insulin dependent, and prone to periods of ketoacidosis; can be familial, follow a viral infection such as mumps; thought to be due to virus-induced or immune destruction of pancreatic islets. SYN type I d. mellitus.

juvenile-onset d., SYN insulin-dependent d. mellitus.

ketosis-prone d., type I or juvenile d. mellitus, in which inadequate treatment leads to development of ketoacidosis.

ketosis-resistant d., type II or adult onset d. mellitus, in which episodes of ketoacidosis rarely occur.

latent d., a mild form of d. mellitus in which the patient displays no overt symptoms, but displays certain abnormal responses to diagnostic procedures, such as an elevated fasting blood glucose concentration or reduced glucose tolerance. Term declared obsolete by American Diabetes Association. SYN chemical d.

lipoatrophic d., SYN lipoatrophy.

lipogenous d., d. and obesity combined.

maturity-onset d., non-insulin-dependent d. mellitus.

maturity onset d. of youth, a relatively mild, non-insulin requiring form of d. mellitus beginning at a younger age than usual.

d. melli'tus (DM), a chronic metabolic disorder in which utilization of carbohydrate is impaired and that of lipid and protein enhanced; it is caused by an absolute or relative deficiency of insulin and is characterized, in more severe cases, by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis, and coma; long-term complications include neuropathy, retinopathy, nephropathy, generalized degenerative changes in large and small blood vessels, and increased susceptibility to infection. [L. sweetened with honey]

diabetes mellitus (DM): etiologic classification

I. Primary diabetes mellitus (types 1 and 2)
II. Secondary diabetes
  A. pancreatic diabetes
    – after total or partial pancreatectomy
    – with extensive destruction of pancreas
    – through tumor or wound
    – pancreatitis, hemochromatosis
  B. extrapancreatic/endocrine diabetes
    – with hypersomatotropism (acromegaly)
    – with hyperadrenalism (Cushing syndrome; Conn syndrome, pheochromocytoma)
    – with hyperthyroidism
    – with glucagonoma
  C. drug-induced diabetes
    (somatotropin, ACTH, adrenocorticoid [steroid diabetes], thyroid hormone)
    – thiazides
III. Rare, exceptional forms of diabetes
  e.g., lipoatrophic diabetes (Lawrence); myatonic diabetes (Prader-Labhart-Willi); disturbance of insulin receptors; DM with certain genetic syndromes

Diabetes mellitus affects at least 16 million Americans, ranks seventh as a cause of death in the United States, and costs the national economy over $100 billion yearly. About 95% of persons with DM have type 2, in which the pancreatic beta cells retain some insulin-producing potential, and the rest have type 1, in which exogenous insulin is required for long-term survival. In type 1 DM, which typically causes symptoms before age 25, an autoimmune process is responsible for beta cell destruction. Type 2 DM is characterized by insulin resistance in peripheral tissues as well as a defect in insulin secretion by beta cells. Insulin regulates carbohydrate metabolism by mediating the rapid transport of glucose and amino acids from the circulation into muscle and other tissue cells, by promoting the storage of glucose in liver cells as glycogen, and by inhibiting gluconeogenesis. The normal stimulus for the release of insulin from the pancreas is a rise in the concentration of glucose in circulating blood, which typically occurs within a few minutes after a meal. When such a rise elicits an appropriate insulin response, so that the blood level of glucose falls again as it is taken into cells, glucose tolerance is said to be normal. The central fact in diabetes mellitus is an impairment of glucose tolerance of such a degree as to threaten or impair health. Revised diagnostic criteria for DM were published by the American Diabetes Association in June 1997. All criteria depend on the glucose concentration of venous plasma. The diagnosis is confirmed when any 2 tests performed on different days yield levels at or above established thresholds: in the fasting state, 126 mg/dL (7.0 mmol/L); 2 hours postprandially (after a 75-g glucose load), or at random, 200 mg/dL (11.1 mmol/L).

Long recognized as an independent risk factor for cardiovascular disease, DM is often associated with other risk factors, including disorders of lipid metabolism, obesity, hypertension, and impairment of renal function. Current recommendations for the management of DM emphasize education and individualization of therapy. Controlled studies have shown that rigorous maintenance of plasma glucose levels as near to normal as possible at all times substantially reduces the incidence and severity of long-term complications, particularly microvascular complications (retinopathy, neuropathy, and nephropathy). Such control involves limitation of dietary carbohydrate and saturated fat; monitoring of blood glucose, including self-testing by the patient and periodic determination of glycosylated hemoglobin; and administration of insulin (particularly in type 1 DM), drugs that stimulate endogenous insulin production (in type 2 DM), or both. Some studies suggest that the risk of cardiovascular disease may be increased in some patients by intensive treatment of DM because of elevation of body weight, blood pressure, triglycerides, and total and low-density cholesterol. Pharmaceutical agents developed during the 1990s have improved control of DM by enhancing responsiveness of cells to insulin, counteracting insulin resistance, and reducing postprandial carbohydrate absorption. See Also insulin resistance; alpha-reductase inhibitor.

metahypophysial d., (1) d. mellitus caused by large quantities of endogenous or exogenous pituitary growth hormone; (2) term used to designate the irreversible phase of d. mellitus in acromegaly.

Mosler d., inosituria with excretion of large quantities of water.

nephrogenic d. insipidus [MIM*304800], d. insipidus due to inability of the kidney tubules to respond to antidiuretic hormone; X-linked inheritance, caused by mutation in the vasopressin V2 receptor gene (AVPR2) on Xq. There is also an autosomal dominant form [MIM*125800], caused by mutation in the aquaphorin 2 gene (AQP2) on 12q. SYN vasopressin-resistant d.

non-insulin-dependent d. mellitus (NIDDM), an often mild form of d. mellitus of gradual onset, usually in obese individuals over age 35; absolute plasma insulin levels are normal to high, but relatively low in relation to plasma glucose levels; ketoacidosis is rare, but hyperosmolar coma can occur; responds well to dietary regulation and/or oral hypoglycemic agents, but diabetic complications and degenerative changes can develop. Term declared obsolete by American Diabetes Association.

pancreatic d., (1) d. mellitus demonstrably dependent upon a pancreatic lesion; (2) d. following removal of the pancreas in an animal.

phlorizin d. (flō-rid'zin). SYN phlorizin *glycosuria.*

phosphate d., excessive secretion of phosphate in the urine due to a defect in tubular reabsorption; usually part of a more generalized abnormality, such as Fanconi syndrome.

piqûre d., SYN puncture d. [Fr.]

pregnancy d., SEE subclinical d.

puncture d., experimental d. produced in animals by puncture of the floor of the fourth ventricle of the brain. SYN piqûre d.

renal d., SYN renal *glycosuria.*

starvation d., after prolonged fasting; glycosuria following the ingestion of carbohydrate or glucose because of reduced output of insulin and/or reduced rate of glucose metabolism with a reduced ability to form glycogen.

steroid d., d. mellitus produced by pharmacological doses of steroid hormones, particularly glucocorticoids or estrogens; characterized by one or more of the typical manifestations of d. mellitus.

steroidogenic d., abnormal glucose tolerance, often frank d. mellitus, induced by the metabolic effects of adrenocortical steroid hormones such as cortisone or therapeutic analogues such as prednisone. The effect may be temporary, resolving when the steroid therapy is discontinued, or d. mellitus may persist.

subclinical d., a form of d. mellitus that is clinically evident only under certain circumstances, such as pregnancy or extreme stress; persons so afflicted may, in time, manifest more severe forms of the disease. Term declared obsolete by American Diabetes Association.

thiazide d., impaired carbohydrate metabolism associated with the use of thiazide diuretic drugs; severe manifestations are seen in persons having d. mellitus, but impairment is mild or absent in nondiabetic individuals.

type I d., SYN insulin-dependent d. mellitus.

type II d., non-insulin-dependent d. mellitus.

type I d. mellitus, SYN juvenile d.

vasopressin-resistant d., SYN nephrogenic d. insipidus.

di·a·bet·ic (dī-ă-bet'ik). 1. Relating to or suffering from diabetes. 2. One who suffers from diabetes.

di·a·be·to·gen·ic (dī'ă-bet-ō-jen'ik, -bē-tō-jen'ik). Causing diabetes.

di·a·be·tog·en·ous (dī'ă-bē-toj'en-ŭs). Caused by diabetes.

di·a·be·tol·o·gy (dī'ă-be-tol'ō-jē). The field of medicine concerned with diabetes.

di·a·cele (dī'ă-sēl). Rarely used term for third *ventricle.* [G. *dia-,* through, + *koilia,* a hollow]

di·ac·e·tal (dī-as'ĕ-tal). SEE diacetyl.

di·ac·e·tate (dī-as'ĕ-tāt). 1. SYN acetoacetate. 2. A compound containing two acetate residues.

di·ac·e·te·mia (dī-as-ĕ-tē'mē-ă). A form of acidosis resulting from the presence of acetoacetic (diacetic) acid in the blood.

di·ac·e·ton·u·ria (dī-as'ĕ-tō-noo'rē-ă). SYN diaceturia.

di·ac·e·tu·ria (dī-as-ĕ-too'rē-ă). The urinary excretion of acetoacetic (diacetic) acid. SYN diacetonuria.

di·a·ce·tyl, di·ac·e·tal (dī-as'ĕ-til, dī-as'ĕ-tal). A yellow liquid, $(CH_3CO)_2$, having the pungent odor of quinone and carrying the aromas of coffee, vinegar, butter, and other foods; a byproduct of carbohydrate degradation.

di·a·ce·tyl·cho·line (dī-as'ĕ-til-kō'lēn). SYN succinylcholine.

di·a·ce·tyl·mon·ox·ime (DAM) (dī-as'ĕ-til-mon-ok'sim). A 2-oxo-oxime that can reactivate phosphorylated acetylcholinesterase in vitro and in vivo; it penetrates the blood-brain barrier. Similar to 2-PAM.

di·a·ce·tyl·mor·phine (dī-as'ĕ-til-mōr'fēn). SYN heroin.

di·a·ce·tyl·tan·nic ac·id (dī-as'ĕ-til-tan'ik). SYN acetyltannic acid.

di·a·chron·ic (dī-ă-kron'ik). Systematically observed over time in the same subjects throughout as opposed to synchronic or cross-sectional; the inferences are equivalent only where there is strict stability of all elements. [dia- + G. *chronos,* time]

di·ac·id (dī-as'id). Denoting a substance containing two ionizable hydrogen atoms per molecule; more generally, a base capable of combining with two hydrogen ions per molecule.

di·ac·la·sis, di·a·cla·sia (dī-ak'lă-sis, dī-ă-klā'zē-ă). SYN osteoclasis. [G. *diaklasis,* a breaking up. fr. *dia,* through, + *klasis,* a breaking]

di·ac·ri·nous (dī-ak'ri-nŭs). Excreting by simple passage through a gland cell. [G. *diakrinō,* to separate one from another]

di·ac·ri·sis (dī-ak'ri-sis). SYN diagnosis. [G. *dia-,* through, + *krisis,* a judgment]

di·a·crit·ic, di·a·crit·i·cal (dī-ă-krit'ik, -krit'i-kăl). Distinguishing; diagnostic; allowing of distinction. [G. *diakritikos,* able to distinguish]

di·ac·tin·ic (dī'ak-tin'ik). Having the property of transmitting light capable of bringing about chemical reactions. [G. *dia,* through, + *aktis,* ray]

di·ac·yl·glyc·er·ol (DAG) (dī'as-il-glis'er-ol). Diglyceride; glycerol with two esterified acyl moieties, either 1,3-d. or 1,2-d.; if the two acyl groups are nonidentical, there are four possible stereoisomers; 1,2-d. is an intermediate in the synthesis of triacylglycerols and of lecithin; also serves as a second messenger in stimulating the activity of protein kinase C.

d. acyltransferase, an enzyme, in fat biosynthesis, that catalyzes the transfer of an acyl moiety from acyl-CoA to 1,2-d. thus forming free coenzyme A and triacylglycerol.

d. lipase, SYN lipoprotein lipase.

di·ad (dī'ad). 1. The transverse tubule and a cisterna in cardiac muscle fibers. 2. SYN dyad (1).

di·ad·o·cho·ci·ne·sia (dī-ad'ō-kō-si-nē'zē-ă). SYN diadochokinesia.

di·ad·o·cho·ki·ne·sia, di·ad·o·cho·ki·ne·sis (dī-ad'ō-kō-ki-nē'zē-ă, -ki-nē'sis). The normal power of alternately bringing a limb into opposite positions, as of flexion and extension or of pronation and supination. SYN diadochocinesia. [G. *diadochos,* working in turn, + *kinēsis,* movement]

di·ad·o·cho·ki·net·ic (dī-ad'ō-kō-ki-net'ik). Relating to diadochokinesia.

di·ag·nose (dī-ag-nōs'). To make a diagnosis.

di·ag·no·sis (dī-ag-nō'sis). The determination of the nature of a disease, injury, or congenital defect. SYN diacrisis. [G. *diagnōsis,* a deciding]

antenatal d., SYN prenatal d.

clinical d., a d. made from a study of the signs and symptoms of a disease.

differential d., the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings. SYN differentiation (2).

d. by exclusion, a d. made by excluding those diseases to which only some of the patient's symptoms might belong, leaving one disease as the most likely d., although no definitive tests or findings establish that d.

laboratory d., a d. made by a chemical, microscopic, microbiologic, immunologic, or pathologic study of secretions, discharges, blood, or tissue.

neonatal d., systematic evaluation of the newborn for evidence of disease or malformations, and the conclusion reached.

pathologic d., a d., sometimes postmortem, made from an anatomic and/or histologic study of the lesions present.

physical d., (1) a d. made by means of physical examination of the patient. (2) the process of a physical examination.

prenatal d., d. utilizing procedures available for the recognition of diseases and malformations *in utero*, and the conclusion reached. SYN antenatal d.

di·ag·nos·tic (dī-ag-nos'tik). **1.** Relating to or aiding in diagnosis. **2.** Establishing or confirming a diagnosis.

di·ag·nos·ti·cian (dī'ag-nos-tish'ăn). One who is skilled in making diagnoses; formerly, a name for specialists in internal medicine.

***Diagnostic and Statistical Manual of Mental Disorders* (DSM).** A system of classification, published by the American Psychiatric Association, that divides recognized mental disorders into clearly defined categories based on sets of objective criteria. Representing a majority view (rather than a consensus) of hundreds of contributors and consultants, DSM is widely recognized as a diagnostic standard and widely used for reporting, coding, and statistical purposes.

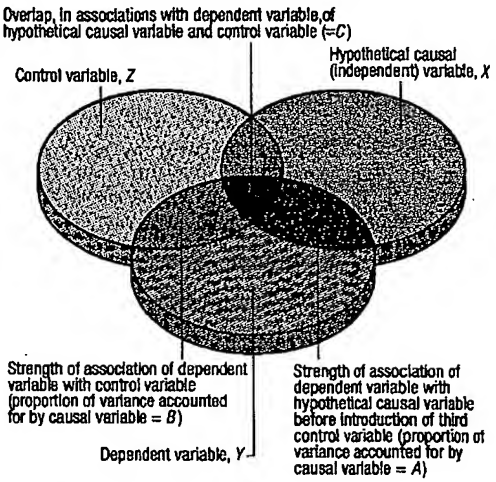
The first edition (1952), based on the sixth revision of the *International Classification of Diseases* (*ICD-6*), was intended to promote uniformity in the naming and reporting of psychiatric disorders. It contained definitions of all named disorders, but no sets of diagnostic criteria. While its classification of mental disorders showed the influence of Freudian psychoanalysis, its nomenclature (e.g., depressive reaction, anxiety reaction, schizophrenic reaction) reflected the theories of Adolf Meyer (1866–1950). The second edition (*DSM-II*, 1968) preserved the psychoanalytic orientation but dropped the "reaction" terminology. The third edition (*DSM-III*, 1980) abandoned much of the rigidly psychodynamic thinking of the earlier editions and, for the first time, provided explicit diagnostic criteria and introduced a multiaxial system whereby different aspects of a patient's condition could be separately assessed. Briefly stated, the axes are I, clinical disorders; II, personality disorders and mental retardation; III, general medical disorders; IV, psychosocial and environmental stressors; and V, overall level of functioning. A revised version of the third edition (*DSM-IIIR*, 1987) incorporated a number of improvements and clarifications. The fourth edition (*DSM-IV*) appeared in May, 1994. It follows its two predecessors closely in general outline, and like them is coordinated with and partly derived from *ICD-9*. For many observers, the most significant change in *DSM-IV* is the renaming of the category formerly called "Organic Mental Syndromes and Disorders" as "Delirium, Dementia, and Amnestic and Other Cognitive Disorders," a shift in terminology intended to avoid the implication that mental disorders in other categories are not organic.

di·a·gram. A simple, graphic depiction of an idea or object.

Dieuaide d., SYN triaxial reference *system*.

flow d., a d. composed of blocks connected by arrows representing steps in a process such as decision analysis.

Venn d., pictorial representation of the extent to which two or more quantities or concepts are mutually inclusive and exclusive.



Venn diagram

di·a·ki·ne·sis (dī'ă-ki-nē'sis). Final stage of prophase in meiosis I, in which the chiasmata present during the diplotene stage disappear, the chromosomes continue to shorten, and the nucleolus and nuclear membrane disappear. [G. *dia*, through, + *kinēsis*, movement]

dial (dī'ăl, dīl). A clock face or instrument resembling a clock face. [L. *dies*, day]

astigmatic d., a diagram of radiating lines, used to test for astigmatism.

Di·a·lis·ter (dī-ăl-is'ter). An obsolete name for a genus of bacteria, the type species of which, *D. pneumosintes*, is now placed in the genus *Bacteroides*.

di·al·lyl (dī-al'il). A compound containing two allyl groups.

di·al·y·sance (dī-al'i-sans). The number of milliliters of blood completely cleared of any substance by an artificial kidney or by peritoneal dialysis in a unit of time; conventional clearance formulas are expressed as mm/min. [fr. dialysis]

di·al·y·sate (dī-al'i-sāt). That part of a mixture that passes through a dialyzing membrane; the material that does not pass through is referred to as the retentate. SYN diffusate.

di·al·y·sis (dī-al'i-sis). **1.** A form of filtration to separate crystalloid from colloid substances (or smaller molecules from larger ones) in a solution by interposing a semipermeable membrane between the solution and dialyzing fluid; the crystalloid (smaller) substances pass through the membrane into the dialyzing fluid on the other side, the colloids do not. **2.** The separation of substances across a semipermeable membrane on the basis of particle size and/or concentration gradients. **3.** A method of artificial kidney function. [G. a separation, fr. *dialyo*, to separate]

continuous ambulatory peritoneal d. (CAPD), method of peritoneal d. performed in ambulatory patients with influx and efflux of dialysate during normal activities.

equilibrium d., in immunology, a method for determination of association constants for hapten-antibody reactions in a system in which the hapten (dialyzable) and antibody (nondialyzable) solutions are separated by semipermeable membranes. Since at equilibrium the quantity of free hapten will be the same in the two compartments, quantitative determinations can be made of hapten-bound antibody, free antibody, and free hapten.

extracorporeal d., hemodialysis performed through an apparatus outside the body.

peritoneal d., removal from the body of soluble substances and

as the presynaptic (preganglionic) neuron, the thin but myelinated axon of which (presynaptic (preganglionic) or B fiber) emerges with an outgoing spinal or cranial nerve and synapses with one or more of the postsynaptic (postganglionic or, more strictly, ganglionic) neurons composing the autonomic ganglia; the unmyelinated postsynaptic fibers in turn innervate the smooth muscle, cardiac muscle, or gland cells. The presynaptic neurons of the sympathetic part lie in the intermediolateral cell column of the thoracic and upper two lumbar segments of the spinal gray matter; those of the parasympathetic part compose the visceral motor (visceral efferent) nuclei of the brainstem as well as the lateral column of the second to fourth sacral segments of the spinal cord. The ganglia of the sympathetic part are the paravertebral ganglia of the sympathetic trunk and the lumbar and sacral prevertebral or collateral ganglia; those of the parasympathetic part lie either near the organ to be innervated or as intramural ganglia within the organ itself except in the head, where there are four discrete parasympathetic ganglia (ciliary, otic, pterygopalatine, and submandibular). Impulse transmission from presynaptic to postsynaptic neuron is mediated by acetylcholine in both the sympathetic and parasympathetic parts; transmission from the postsynaptic fiber to the visceral effector tissues is classically said to be by acetylcholine in the *parasympathetic part* and by *noradrenalin* in the sympathetic part; recent evidence suggests the existence of further noncholinergic, nonadrenergic classes of postsynaptic fibers. SYN divisio autonomica systematis nervosi periphérici [TA], pars autonomica systematis nervosi peripherici [TA], autonomic part of peripheral nervous system★, autonomic nervous system, involuntary nervous system, systema nervosum autonomicum, vegetative nervous system, visceral motor system, visceral nervous system.

cleavage d., the rapid mitotic d. of the zygote with decrease in size of individual cells or blastomeres and the formation of a morula. SEE ALSO cleavage (1).

conjugate d., simultaneous d. of haploid nuclei, as in Basidiomycota.

craniosacral d. of autonomic nervous system, SYN parasympathetic *part* of autonomic division of peripheral nervous system.

direct nuclear d., SYN amitosis.

equatorial d., nuclear d. *in which* each chromosome divides equally.

indirect nuclear d., SYN mitosis.

lateral d. of left liver, ★official alternate term for left *lobe* of liver.

left lateral d. of liver [TA], in the surgical schema for subdividing the liver, the portion that lies to the left of the approximately vertical plane of the left hepatic vein and includes the left posterior and anterior lateral segments (hepatic segments II and III); it corresponds with the left anatomic lobe of the liver, and so is demarcated externally by the falciform ligament on the diaphragmatic surface and by the fissures for the ligamentum venosum and ligamentum teres on the viscera surface. SYN divisio lateralis sinistra hepatis [TA].

left medial d. of liver [TA], in the surgical schema for subdividing the liver, the portion that lies between the approximately vertical planes of the left and middle hepatic veins and includes the left medial segment (hepatic segment IV); on the diaphragmatic surface, it is approximately the left third of the anatomic right lobe of the liver; on the visceral surface, its inferior portion corresponds to the quadrate lobe. SYN divisio medialis sinistra hepatis [TA].

meiotic d., SYN meiosis.

mitotic d., SYN mitosis.

multiplicative d., reproduction by simultaneous d. of a mother cell into a number of daughter cells. If the process occurs without fertilization of the mother cell, or encystment, the daughter cells are called merozoites; if they develop within a cyst, and usually after fertilization, they are called sporozoites.

posterior primary d., SYN posterior *ramus* of spinal nerve.

posterior d.'s of (trunks of) brachial plexus [TA], portion of the superior, middle, and inferior trunks of the brachial plexus that are destined to serve the posterior or extensor compartments of the upper limb. SYN divisiones posteriores plexus brachialis [TA].

reduction d., SEE *reduction* of chromosomes.

Remak nuclear d., SYN amitosis.

right lateral d. of liver [TA], in the surgical schema for subdividing the liver, the portion that lies to the right of the approximately vertical plane of the right hepatic vein and includes the right anterior and posterior lateral segments (hepatic segments VI and VII); it is approximately the right third of the right anatomic lobe of the liver. SYN divisio lateralis dextra hepatis [TA].

right medial d. of liver [TA], in the surgical schema for subdividing the liver, the portion that lies between the approximately vertical planes of the right and middle hepatic veins and includes the right anterior and posterior medial segments (hepatic segments V and VIII); it is approximately the middle third of the anatomic right lobe of the liver. SYN divisio medialis dextra hepatis [TA].

div. in p. aeq. Abbreviation for L. *divide in partes aequales*, divide into equal parts.

di·vulse (di-vŭls'). To tear away or apart. [L. *divello*, pp. *di-vulsus*, to pull apart]

di·vul·sion (di-vŭl'shŭn). **1.** Removal of a part by tearing. **2.** Forcible dilation of the walls of a cavity or canal.

di·vul·sor (di-vŭl'sĕr, -sōr). An instrument for forcible dilation of the urethra or other canal or cavity.

Dix, M.R., 20th century British otologist. SEE Dix-Hallpike *maneuver*.

di·xyr·a·zine (dī-zir'ă-zēn). A phenothiazine compound used as an antipsychotic.

di·zy·got·ic, di·zy·gous (dī'zī-got'ik, dī-zī'gŭs). Relating to twins derived from two separate zygotes, i.e., bearing the same genetic relationship as full sibs but sharing a common intrauterine environment. [G. *di-*, two, + *zygotos*, yoked together]

diz·zi·ness (diz'i-nes). Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness, or vertigo. SEE ALSO vertigo. [A.S. *dysig*, foolish]

djen·kol·ic ac·id (jeng-kol'ik). *S,S'*-Methylenebiscysteine; a sulfur-containing amino acid, resembling cystine but with a methylene bridge between the two sulfur atoms; very insoluble. [*djenkol* bean, bean in which first isolated]

△**DL-.** Prefix (in small capital letters) denoting a substance consisting of equal quantities of the two enantiomorphs, D and L; replaces the older *dl-* as a more exact definition of structure.

***dl*-nar·co·tine** (nar'kō-tēn). SYN gnoscopine.

DM Abbreviation for adamsite; *diabetes* mellitus; diastolic *murmur*; dopamine.

DMA Abbreviation for dimethoxyamphetamine.

DMARD Acronym for disease modifying antirheumatic *drugs*, under *drug*.

DMC Abbreviation for *p,p'*-dichlorodiphenyl methyl carbinol.

D.M.D. Abbreviation for Doctor of Dental Medicine.

dmf, DMF Abbreviation for decayed, missing, and filled teeth. SEE ALSO dmfs caries *index*.

dmfs, DMFS Abbreviation for decayed, missing, and filled surfaces. SEE ALSO *dmfs caries index*.

DMPP Abbreviation for dimethylphenylpiperazinium.

DMSA. SEE ^{99m}Tc-dimercaptosuccinic acid.

DMSO Abbreviation for dimethyl sulfoxide.

DMT Abbreviation for *N,N*-dimethyltryptamine.

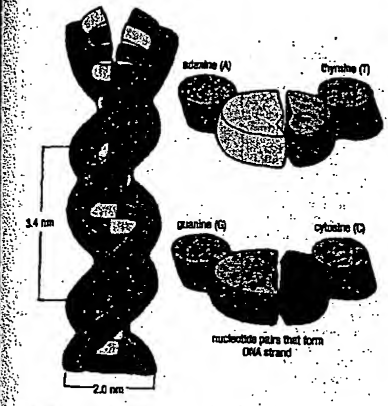
DN Abbreviation for dibucaine number.

DNA Abbreviation for deoxyribonucleic acid. For terms bearing this abbreviation, see subentries under deoxyribonucleic acid.

DNA diagnostics. SYN genetic *testing*. SEE DNA markers, familial *screening*, prenatal *screening*.

dnaG SYN primase.

DNA markers. Segments of chromosomal DNA known to be linked with heritable traits or diseases. Although the markers themselves do not produce the conditions, they exist in concert with the genes responsible and are passed on with them. Certain markers, restriction fragment length polymorphisms, consist of segments of DNA that can be identified on autoradiographs (produced after digestion of the DNA by restriction enzymes and segregation of the resulting fragments through gel electrophoresis).



DNA (deoxyribonucleic acid)

DNAse, DNAase, DNase Abbreviations for deoxyribonuclease.

DNP, Dnp 1. Abbreviation for 2,4-dinitrophenol. 2. Abbreviation for deoxyribonucleoprotein.

DNR Abbreviation for "do not resuscitate."

Dns, DNS Abbreviations for dansyl.

D.O. Abbreviation for Doctor of Osteopathy.

DOA Abbreviation for dead on arrival.

do·bu·ta·mine (dō-bū'tă-mēn). A synthetic derivative of dopamine characterized by prominent inotropic but weak chronotropic and arrhythmogenic properties; a cardiotonic agent.

DOC Abbreviation for deoxycorticosterone; deoxycholate.

d'Ocagne, Philbert M., French mathematician, 1862–1938. SEE d'O. *nomogram*.

***n*-doc·o·sa·no·ic ac·id** (dō'kō-san-ō'ik). SYN behenic acid.

doc·tor (dok'ter). **1.** A title conferred by a university on one who has followed a prescribed course of study, or given as a title of distinction; as d. of medicine, laws, philosophy, etc. **2.** A physician, especially one upon whom has been conferred the degree of M.D. by a university or medical school. [L. a teacher, fr. *doceo*, pp. *doctus*, to teach]

doc·trine (dok'trin). A particular system of principles taught or advocated. [L. *doceo*, to teach]

Arrhenius d., the theory of electrolytic dissociation (1887) that became the basis of our modern understanding of electrolytes: in an electrically conductive solution (e.g., acid, base, or salt), free ions are present before electrolysis, and the proportion of molecules dissociated into ions can be calculated from measurements of electrical conductivity as well as of osmotic pressure. SYN Arrhenius law.

humoral d., the ancient Greek theory of the four body humors (blood, yellow and black bile, and phlegm) that determined health and disease. The humors were associated with the four elements (air, fire, earth, and water), which in turn were paired with one of the qualities (hot, cold, dry, and moist). A proper and evenly balanced mixture of the humors characterized health of body and mind; an imperfect balance resulted in disease. Temperament of body or mind also was supposed to be determined, e.g., sanguine (blood), choleric (yellow bile), melancholic (black bile), or phlegmatic (phlegm). SYN fluidism, humoralism, humorism.

Monro d., a d. that states that the cranial cavity is a closed rigid box and that therefore a change in the quantity of intracranial blood can occur only through the displacement of or replacement by cerebrospinal fluid. SYN Monro-Kellie d.

Monro-Kellie d., SYN Monro d.

doc·u·sate cal·ci·um (dok'ū-sāt). A surface-active agent used in the treatment of constipation as a nonlaxative fecal softener. SYN dioctyl calcium sulfosuccinate.

doc·u·sate so·di·um. A surface-active agent used as a dispersing agent in topically applied preparations. After oral administration it lowers the surface tension of the gastrointestinal tract and is used in the treatment of constipation as a wetting agent and stool softener. SYN dioctyl sodium sulfosuccinate.

do·de·cane (dō'dĕ-kān). *n*-$C_{12}H_{26}$; a straight, unbranched, saturated hydrocarbon containing 12 carbon atoms; the 12th member of the alkane series that begins with methane.

***n*-do·dec·a·no·ic ac·id** (dō-dek'ă-nō-ik). SYN lauric acid.

do·dec·an·o·yl-CoA syn·the·tase (dō-dek'ăn-ō-il-kō-ā sin'thĕ-tās). SYN long-chain fatty acid-CoA ligase.

do·de·car·bo·ni·um chlo·ride (dō-dĕ-kar-bō'nē-ŭm). An antiseptic.

do·de·cyl (dō'dĕ-sil). The radical of dodecane.

d. gallate, an antioxidant.

d. sulfate, SEE *sodium* dodecyl sulfate.

Döderlein, Albert, S.G., German obstetrician, 1860–1941. SEE D. *bacillus*.

Doerfler, Leo G., U.S. audiologist, *1919. SEE D.-Stewart *test*.

Dogiel, Alexander S., Russian histologist, 1852–1922. SEE D. *corpuscle*.

Dogiel, Jan von, Russian anatomist and physiologist, 1830–1905. SEE D. *cells*, under *cell*.

dog·ma. A theory or belief that is formally stated, defined, and thought to be true.

central d., the proposition that while genetic information is transferred from parent to offspring via DNA duplication, within the cell, genetic information is transferred from DNA to mRNA (transcription) and then to protein (translation); proposed by Francis Crick.

dog·mat·ic (dog-mat'ik). SEE dogmatic *school*. [G. *dogmatikos*, concerning opinions; *d. iatroi*, physicians who go by general principles; fr. *dogma*, an opinion]

dog·ma·tist (dog'mă-tist). A follower of the dogmatic *school*.

Döhle, Karl G.P., German histologist and pathologist, 1855–1928. SEE D. *bodies*, under *body*, *inclusions*, under *inclusion*.

Doisy, Edward A., U.S. biochemist and Nobel laureate, 1893–1986. SEE Allen-D. *test*, *unit*.

dol (dōl). A unit measure of pain. [L. *dolor*, pain]

△**dolicho-.** Long. [G. *dolichos*]

dol·i·cho·ce·phal·ic, dol·i·cho·ceph·a·lous (dol-i-kō-sĕ-fal'ik, -sef'ă-lŭs). Having a disproportionately long head; denoting a skull with a cephalic index below 75. SYN dolichocranial. [dolicho- + G. *kephalē*, head]

dol·i·cho·ceph·a·ly, dol·i·cho·ceph·a·lism (dol-i-kō-sef'ă-lē, sef'ă-lizm). The condition of being dolichocephalic.

dol·i·cho·co·lon (dol-i-kō-kō'lŏn). A colon of abnormal length. [dolicho- + G. *kōlon*, colon]

dol·i·cho·cra·ni·al (dol-i-kō-krā'nē-ăl). SYN dolichocephalic.

dol·i·cho·fa·cial (dol-i-kō-fā'shăl). SYN dolichoprosopic.

dol·i·chol (dol'i-kol). Polyisoprenes in which the terminal member is saturated and oxidized to an alcohol, usually phosphorylated and often glycosylated; found in endoplasmic reticulum, but not in mitochondrial or plasma membranes; urinary levels are elevated in disorders exhibiting abnormal skin, rectal, or brain profiles in electron microscopy of biopsies.

d. phosphate, an intermediate in the glycosylation of proteins and lipids; contains 11–24 isoprene units; a product of the isoprenylation pathway; participates in the formation of glycosylphosphatidylinositol anchors of proteins in biomembranes.

therapeutic i., the ratio of LD_{50} to ED_{50}, used in quantitative comparison of drugs.

thoracic i., anteroposterior diameter of the thorax times 100 divided by the transverse diameter of the thorax. SYN chest i.

tibiofemoral i., the ratio obtained by multiplying the length of the tibia by 100 and dividing by the length of the femur.

transversovertical i., SYN vertical i.

tuberculoopsonic i., the opsonic i. calculated in relation to tuberculous infection, with an actively growing culture of *Mycobacterium tuberculosis* or the strain of tubercle bacillus from the patient being used in the test.

ultraviolet i., a daily i. issued by the U.S. National Weather Service for many cities, forecasting the amount of dangerous ultraviolet light that will arrive at the earth's surface about noon the following day.

uricolytic i., the percentage of uric acid oxidized to allantoin before being secreted.

vertical i., the relation of the height to the length of the skull: (height × 100)/length. SYN height-length i., length-height i., transversovertical i.

vital i., the ratio of births to deaths within a population during a given time.

Volpe-Manhold i. (V-MI), an index for comparing the amount of dental calculus in individuals.

volume i., an indication of the relative size (e.g., volume) of erythrocytes, calculated as follows: hematocrit value, expressed as per cent of normal ÷ red blood cell count, expressed as per cent of normal = volume i.

zygomaticoauricular i., the ratio between the zygomatic and the auricular diameters of the skull or head.

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in·di·can (in'di-kan). **1.** Indoxyl β-D-glucoside from *Indigofera* species and *Polygonium tinctorium;* a source of indigo. SYN plant i. **2.** 3-Indoxylsulfuric acid, a substance found (as its salts) in sweat and in variable amounts in urine; indicative, when in quantity, of protein putrefaction in the intestine (indicanuria). SYN metabolic i., uroxanthin.

metabolic i., SYN indican (2).

plant i., SYN indican (1).

in·di·can·i·dro·sis (in'di-kan-i-drō'sis). Excretion of indican in the sweat. [indican + G. *hidrōs*, sweat]

in·di·cant (in'di-kant). **1.** Pointing out; indicating. **2.** An indication; especially a symptom indicating the proper line of treatment. [L. *in-dico*, pres. p. *-ans* (*-ant*), to point out]

in·di·can·u·ria (in'di-kan-ū'rē-ă). An increased urinary excretion of indican, a derivative of indol formed chiefly in the intestine when protein is putrefied; indol is also formed during the putrefaction of protein in other sites.

in·di·ca·tion (in-di-kā'shŭn). The basis for initiation of a treatment for a disease or of a diagnostic test; may be furnished by a knowledge of the cause (**causal i.**), by the symptoms present (**symptomatic i.**), or by the nature of the disease (**specific i.**). [L. fr. *in-dico*, pp. *-atus*, to point out, fr. *dico*, to proclaim]

off label i., use of a medication for a purpose other than that approved by the FDA.

in·di·ca·tor (in'di-kā-ter, -tōr). **1.** In chemical analysis, a substance that changes color within a certain definite range of pH or oxidation potential, or in any way renders visible the completion of a chemical reaction; e.g., litmus, phenolsulfonphthalein. **2.** An isotope that is used as a tracer. **3.** The labeled substance whose distribution between reactants of a system is used to determine the amount of analyte present. [L. one that points out]

alizarin i., a solution consisting of 1 g sodium alizarin sulfonate dissolved in 100 mL distilled water; used as an i. for free acidity in gastric contents.

clinical i., a measure, process, or outcome used to judge a particular clinical situation and indicate whether the care delivered was appropriate.

health i., variable, susceptible to direct measurement, that reflects the state of health of persons in a community.

oxidation-reduction i., a substance that undergoes a definite color change at a specific oxidation potential. SYN redox i.

redox i., SYN oxidation-reduction i.

in·di·ces (in'di-sēz). Alternative plural of index.

In·di·el·la (in-dē-el'ă). Old name for *Madurella*.

in·dig·e·nous (in-dij'ĕ-nŭs). Native; natural to the country or region where found. [L. *indigenus*, born in fr. *indu*, within (old form of *in*), + G. *-gen*, producing]

in·di·ges·tion (in-di-jes'chŭn). Nonspecific term for a variety of symptoms resulting from a failure of proper digestion and absorption of food in the alimentary tract.

acid i., i. resulting from hyperchlorhydria; often used by the laity as a synonym for pyrosis.

fat i., SYN steatorrhea.

gastric i., SYN dyspepsia.

nervous i., i. caused by emotional upsets or stress.

in·di·go (in'dĭ-gō) [C.I. 73000]. A blue dyestuff obtained from *Indigofera tinctoria*, and other species of *Indigofera* (family Leguminosae); also made synthetically. SYN indigo blue, indigotin. [L. *indicum*, fr. G. *indikon*, indigo, ntr. of *Indikos*, Indian]

in·di·go blue. SYN indigo.

in·di·go car·mine [C.I. 73015]. A blue dye used for measurement of kidney function and as a special stain for Negri bodies. SYN sodium indigotin disulfonate.

in·dig·o·tin (in-dig'ō-tin, in-di-gō'tin). SYN indigo.

in·di·go·u·ria, in·di·gu·ria (in'dī-gō-ū'rē-ă, in-di-goo'rē-ă). The excretion of indigo in the urine.

in·dis·po·si·tion (in-dis-pō-zish'ŭn). Illness, usually slight; malaise. [L. *in* neg. + *dispositio*, an arrangement, fr. *dis-pono*, pp. *-positus*, to place apart]

in·di·um (In) (in'dē-ŭm). A metallic element, atomic no. 49, atomic wt. 114.82. [*indigo*, because of its blue line in the spectrum]

in·di·um-111 (^{111}In). A cyclotron-produced radionuclide with a half-life of 2.8049 days and with gamma ray emissions of 171.2 and 245.3 kiloelectron volts. In a chloride form, it is used as a bone marrow and tumor-localizing tracer; in a chelate form, as a cerebrospinal fluid tracer. It is also used as a white blood cell labeling agent and as an antibody label.

i. chloride, i. trichloride, $InCl_3$; used in electron microscopy to stain nucleic acids in thin tissue sections.

in·di·um-113m (^{113m}In). A radioactive isomer of ^{113}In; it has a half-life of 1.658 hours; it has been used in cisternography and as a diagnostic aid in cardiac output.

in·di·vid·u·a·tion (in'di-vid-ū-ā'shŭn). **1.** Development of the individual from the specific. **2.** In jungian psychology, the process by which one's personality is differentiated, developed, and expressed. **3.** Regional activity in an embryo as a response to an organizer.

in·do·cy·a·nine green (in-dō-sī'ă-nēn). A tricarbocyanine dye that binds to serum albumin and is used in blood volume determinations and in liver function tests.

in·do·cy·bin (in-dō-sī'bin). SYN psilocybin.

in·dol·ac·e·tu·ria (in'dōl-as-ĕ-too'rē-ă). Excretion of an appreciable amount of indoleacetic acid in the urine; a manifestation of Hartnup disease, also seen in patients with carcinoid tumors.

in·dol·a·mine (in-dol'ă-mēn). General term for an indole or indole derivative containing a primary, secondary, or tertiary amine group (e.g., serotonin).

in·dole (in'dōl). **1.** 2,3-Benzopyrrole; basis of many biologically active substances (e.g., serotonin, tryptophan); formed in degradation of tryptophan. SYN ketole. **2.** Any of many alkaloids containing the i. (1) structure.

in·do·lent (in'dō-lent). Inactive; sluggish; painless or nearly so, said of a morbid process. [L. *in-* neg. + *doleo*, pr. p. *dolens* (*-ent-*), to feel pain]

in·dol·ic ac·ids (in-dōl'ik). Metabolites of L-tryptophan formed within the body or by intestinal microorganisms; the principal i. a. encountered in urine are indoleacetic acid, indoleacetylglutamine, 5-hydroxyindoleacetic acid, and indolelactic acid.

m. fibula'ris pedis, *official alternate term for lateral *border* of foot.

m. frontalis [TA], SYN frontal *border*.

m. frontalis ossis parietalis [TA], SYN frontal *border* of parietal bone.

m. frontalis ossis sphenoidalis [TA], SYN frontal *margin* of sphenoid.

m. incisa'lis [TA], SYN incisal *margin*.

m. inferior [TA], SYN inferior *border*.

m. inferior cer'ebri, SYN inferolateral *margin* of cerebral hemisphere.

m. inferior corporis pancreatis [TA], SYN inferior *border* of body of pancreas.

m. inferior corporis splenis, SYN inferior *border* of body of pancreas.

m. inferior hep'atis [TA], SYN inferior *border* of liver.

m. inferior pancrea'tis, SYN inferior *border* of body of pancreas.

m. inferior pulmo'nis [TA], SYN inferior *border* of lung.

m. inferior splenis [TA], SYN inferior *border* of spleen.

m. inferolatera'lis [TA], SYN inferolateral *margin* of cerebral hemisphere.

m. inferomedia'lis hemispherii cerebri [TA], SYN inferomedial *margin* of cerebral hemisphere.

m. infraorbita'lis, SYN infraorbital *margin*.

m. interosseus [TA], SYN interosseous *border*.

m. interos'seus fib'ulae [TA], SYN interosseous *border* of fibula.

m. interos'seus ra'dii [TA], SYN interosseous *border* of radius.

m. interos'seus tib'iae [TA], SYN interosseous *border* of tibia.

m. interos'seus ul'nae [TA], SYN interosseous *border* of ulna.

m. lacrima'lis maxil'lae [TA], SYN lacrimal *margin* of maxilla.

m. lambdoideus ossis occipitalis [TA], SYN lambdoid *border* of occipital bone.

m. lambdoid'eus squa'mae occipita'lis, SYN lambdoid *border* of occipital bone.

m. lateralis [TA], SYN lateral *border*.

m. latera'lis antebra'chii, *official alternate term for radial *border* of forearm.

m. latera'lis humer'i [TA], SYN lateral *border* of humerus.

m. latera'lis pe'dis [TA], SYN lateral *border* of foot.

m. latera'lis re'nis [TA], SYN lateral *border* of kidney.

m. latera'lis scap'ulae [TA], SYN lateral *border* of scapula.

m. latera'lis un'guis [TA], SYN lateral *border* of nail.

m. liber [TA], SYN free *border*.

m. li'ber ova'rii [TA], SYN free *border* of ovary.

m. li'ber un'guis [TA], SYN free *border* of nail.

m. lin'guae [TA], SYN *margin* of tongue.

m. mastoideus ossis occipitalis [TA], SYN mastoid *border* of occipital bone.

m. mastoi'deus squa'mae occipita'lis, SYN mastoid *border* of occipital bone.

m. media'lis [TA], SYN medial *border*.

m. media'lis antebra'chii, *official alternate term for ulnar *border* of forearm.

m. media'lis cer'ebri, SYN inferomedial *margin* of cerebral hemisphere.

m. media'lis glan'dulae suprarena'lis [TA]; SYN medial *border* of suprarenal gland.

m. media'lis humer'i [TA], SYN medial *border* of humerus.

m. media'lis pe'dis [TA], SYN medial *border* of foot.

m. media'lis re'nis [TA], SYN medial *border* of kidney.

m. media'lis scap'ulae [TA], SYN medial *border* of scapula.

m. media'lis tib'iae [TA], SYN medial *border* of tibia.

m. mesova'ricus ovarii, SYN mesovarian *border* of ovary.

m. nasa'lis os'sis fronta'lis [TA], SYN nasal *margin* of frontal bone.

m. occipita'lis [TA], SYN occipital *border*.

m. occipita'lis os'sis parieta'lis [TA], SYN occipital *border* of parietal bone.

m. occipita'lis os'sis tempora'lis [TA], SYN occipital *margin* of temporal bone.

m. occul'tus un'guis [TA], SYN hidden *border* of nail.

m. orbitalis [TA], SYN orbital *margin*.

m. pal'pebrae [TA], SYN palpebral *margins*, under *margin*.

m. parieta'lis [TA], SYN parietal *border*.

m. parietalis alaris majoris ossis sphenoidalis [TA], SYN parietal *margin* of greater wing of sphenoid.

m. parieta'lis os'sis fronta'lis [TA], SYN parietal *margin* of frontal bone.

m. parieta'lis os'sis sphenoida'lis, SYN parietal *margin* of greater wing of sphenoid.

m. parieta'lis os'sis tempora'lis, SYN parietal *border* of squamous part of temporal bone.

m. parietalis partis squamosae ossis temporalis [TA], SYN parietal *border* of squamous part of temporal bone.

m. poste'rior fib'ulae [TA], SYN posterior *border* of fibula.

m. poste'rior par'tis petro'sae os'sis tempora'lis [TA], SYN posterior *border* of petrous part of temporal bone.

m. poste'rior ra'dii [TA], SYN posterior *border* of radius.

m. poste'rior tes'tis [TA], SYN posterior *border* of testis.

m. poste'rior ul'nae [TA], SYN posterior *border* of ulna.

m. pupilla'ris ir'idis [TA], SYN pupillary *margin* of iris.

m. radia'lis antebra'chii [TA], SYN radial *border* of forearm.

m. sagitta'lis os'sis parieta'lis [TA], SYN sagittal *border* of parietal bone.

m. sphenoida'lis os'sis tempora'lis [TA], SYN sphenoidal *margin* of temporal bone.

m. squamo'sus [TA], SYN squamosal *border*.

m. squamosus alaris majoris ossis sphenoidalis [TA], SYN squamosal *margin* of greater wing of sphenoid.

m. squamo'sus os'sis parieta'lis [TA], SYN squamosal *border* of parietal bone.

m. squamo'sus os'sis sphenoida'lis, SYN squamosal *margin* of greater wing of sphenoid.

m. superior corporis pancreatis [TA], SYN superior *border* of body of pancreas.

m. supe'rior glan'dulae suprarena'lis [TA], SYN superior *border* of suprarenal gland.

m. supe'rior hemispherii cer'ebri [TA], SYN superior *margin* of cerebral hemisphere.

m. supe'rior pancrea'tis, SYN superior *border* of body of pancreas.

m. superior par'tis petro'sae os'sis tempora'lis [TA], SYN superior *border* of petrous part of temporal bone.

m. supe'rior scap'ulae [TA], SYN superior *border* of scapula.

m. supe'rior splenis [TA], SYN superior *border* of spleen.

m. superomedia'lis, SYN superior *margin* of cerebral hemisphere.

m. supraorbita'lis [TA], SYN supraorbital *margin*.

m. tibia'lis pe'dis, *official alternate term for medial *border* of foot.

m. ulna'ris antebra'chii [TA], SYN ulnar *border* of forearm.

m. u'teri [TA], SYN *border* of uterus.

m. zygomat'icus a'lae majo'ris, SYN zygomatic *margin* of greater wing of sphenoid bone.

m. zygomaticus alaris majoris ossis sphenoidalis [TA], SYN zygomatic *margin* of greater wing of sphenoid bone.

Marie, Pierre, French neurologist, 1853–1940. SEE M.-Charcot-M.-Tooth *disease;* Bamberger-M. *disease,* SYN M.-Strümpell *ditease;* Strümpell-M. *disease;* Brissaud-M. *drome;* Foix-Cavany-Marie *syndrome.*

mar·i·hua·na (mar-i-wah'nă). Popular name for the dried flowering leaves of *Cannabis sativa,* which are smoked as cigarettes ("joints," or "reefers." In the U.S. m. includes any part of, extracts from, the female plant. Alternative spellings: marihuana, marijuana. SEE ALSO cannabis. [fr. Sp. *Mariá* Mary-Jane]

Marinesco, Georges, Roumanian neurologist, 1863–1938. SEE M. succulent *hand;* M.-Garland *syndrome;* Marinesco-S. *syndrome.*

mar·i·no·bu·fo·tox·in (mar'i-nō-boo'fō-toks-in). A poison produced by the parotid gland of *Bufo marinus* (family Bufonidae), a large toad native to Central and South America; used in tropical countries for insect control.

Marion, Georges, French urologist, 1869–1932. SEE M. *disease.*

Mariotte, Edmé, French physicist, 1620–1684. SEE M. *bottle, experiment, law,* blind *spot.*

mar·i·po·sis (mär-i-pō'sĕ-s). Thallassoposia; rarely used term for abnormal consumption of sea water as a result of psychogenic factors. SYN thalassoposia. [L. *mare,* the sea, + G. *posis,* drinking]

Marjolin, Jean N., French physician, 1780–1850. SEE M. *ulcer.*

mar·jo·ram (mar'jō-ram). Sweet, leaf, or garden m. whose leaves, with and without a small portion of the flowering tops of *Majorana hortensis* (*Origanum majorana*) (family Labiatae), are used as seasoning and medicinally as a stimulant, carminative, and emmenagogue.

mark. 1. Any spot, line, or other figure on the cutaneous or mucocutaneous surface, visible through difference in color, elevation, or other peculiarity. [A.S. *mearc*]

alignment m., m.'s made in tracings while the kymograph or other recording apparatus is at rest in order to indicate the time relations between two tracings inscribed one above the other, e.g., jugular and radial pulses.

stretch m.'s, SYN *striae* cutis distensae, under *stria.*

mark·er. 1. A device used to make a mark or to indicate measurement. 2. A characteristic or factor by which a cell or molecule can be recognized or identified. 3. A locus containing two or more alleles that, being harmless, are common and therefore yield high frequencies of heterozygotes which facilitate linkage *analysis.*

allotypic m., SYN allotype.

cell m., an identifying characteristic of a cell; e.g., formation of rosettes with sheep erythrocytes as a m. of T lymphocytes, or the presence of surface immunoglobulin as a m. of B lymphocytes.

cell surface m., a surface protein, glycoprotein, or group of proteins that distinguish a cell or subset of cells from another defined subset of cells.

genetic m., SYN genetic *determinant.*

linkage m., a locus at which there is a high probability of heterozygotes (indispensible state for linkage analysis), but in itself perhaps of no clinical interest. SEE ALSO marker *locus.*

necrofetal m., a tumor m. produced by tumor tissue and by fetal tissue of the same type as the tumor, but not by normal adult tissue from which the tumor arises.

polymorphic genetic m., inherited characteristic that occurs within a given population as two or more traits.

time m., an instrument that marks the time, usually in seconds or fractions of seconds, on a kymograph record in physiologic experiments.

tumor m., a substance, released into the circulation by tumor tissue, whose detection in the serum indicates the presence of tumor.

tumor markers used in primary diagnoses

Type of tumor	Marker
testicular carcinoma, choriocarcinoma	β-subunit of human chorionadotropin (β-HCG) and α-1-fetoprotein (AFP)
multiple myeloma	immunoglobulins, Bence Jones protein
neuroblastoma, pheochromocytoma	catecholamines, vanillylmandelic acid, metanephrines
carcinoid	5-hydroxyindoleacetic acid
primary liver cell carcinoma	α-1-fetoprotein
medullary thyroid carcinoma	calcitonin
Hodgkin lymphoma, leukemia	surface antigens

Markov, Andrei, Russian mathematician, 1865–1922. SEE Markov *process.*

Marme re·a·gent. See under reagent.

mar·mo·rat·ed (mar'mō-rā-ted). Denoting a condition in which the appearance of the skin is streaked like marble. SEE ALSO *cutis marmorata.* [L. *marmoratus,* marbled]

mar·mot (mar'mot). A woodchuck or groundhog; a hibernating rodent that may serve as reservoir host of plague bacillus in North America. [Fr. *marmotte*]

Maroteaux, Pierre, French medical geneticist, *1926. SEE M.-Lamy *syndrome.*

Marquis re·a·gent. See under reagent.

mar·row (mar'ō) [TA]. 1. A highly cellular hematopoietic connective tissue filling the medullary cavities and spongy epiphyses of bones; it becomes predominantly fatty with age, particularly in the long bones of the limbs. 2. Any soft gelatinous or fatty material resembling the m. of bone. SEE ALSO medulla. [A.S. *mearh*]

bone m. [TA], the soft, pulpy tissue filling the medullary cavities of bones, having a stroma of reticular fibers and cells; it differs in consistency by age and location. SEE ALSO gelatinous bone m., red bone m., yellow bone m. SYN medulla ossium [TA].

gelatinous bone m. [TA], degenerated marrow of cranial bones in old age.

red bone m. [TA], bone marrow in which the stroma primarily contain the developmental stages of erythrocytes, leukocytes, and megakaryocytes; it is present throughout the skeleton during fetal life and at birth. After the fifth postnatal year, it is gradually replaced in the long bones by yellow marrow. SYN medulla ossium rubra [TA].

spinal m., SYN spinal *cord.*

yellow bone m. [TA], bone m. in which the stroma of the reticular network are largely filled primarily with fat; it replaces red marrow in the long bones after the fifth year of life. SYN medulla ossium flava [TA].

Marshall, Don, U.S. ophthalmologist, *1905. SEE M. *syndrome.*

Marshall, Eli K., U.S. pharmacologist, 1889–1966. SEE M. *method.*

Marshall, John, English anatomist, 1818–1891. SEE M. vestigial *fold,* oblique *vein.*

Marshall, Victor F., U.S. urologist, *1913. SEE M. *test;* M.-Marchetti *test;* M.-Marchetti-Krantz *operation.*

Mar·shal·la·gia mar·shalli (mar-sha-lā'jē-ă mar-shal'ī). One of the medium stomach worms of the nematode family Trichostrongylidae, found in the abomasum of sheep, goats, camels, and various wild ruminants.

marsh·mal·low root (marsh'mal-ō). SYN althea.

mar·su·pi·al (mar-soo'pē-ăl). 1. A member of the order Marsupalia, which includes such mammals as kangaroos, wombats, bandicoots, and opossums, the female of which has an abdominal pouch for carrying the young. 2. Of or pertaining to marsupials. [L. *marsupium,* a pouch]

mar·su·pi·al·i·za·tion (mar-soo'pē-ăl-i-zā'shŭn). Exteriorization of a cyst or other such enclosed cavity by resecting the anterior wall and suturing the cut edges of the remaining wall to adjacent edges of the skin, thereby creating a pouch. [L. *marsupium,* pouch]

mar·su·pi·um (mar-soo'pē-ŭm). 1. SYN scrotum. 2. A pouch or sac; e.g., in marsupials. [L. pouch]

Martegiani, J., 19th century Italian anatomist. SEE M. *area, funnel.*

Martin, August E., German gynecologist, 1847–1933. SEE M. *tube;* M.-Gruber *anastomosis.*

Martin, Henry A., U.S. surgeon, 1824–1884. SEE M. *bandage, disease.*

Martin, J.E. SEE Thayer-M. *medium.*

Martinotti, Giovanni, Italian physician, 1857–1928. SEE M. *cell.*

mar·ti·us yel·low (marsh'ē-ŭs) [C.I. 10315]. An acid dye used as a stain in plant and animal histology, and as a light filter for photomicrography. [Karl A. *Martius,* Ger. chemist, *1920].

difficult for patients to make informed choices about their care. Patients should be told who is providing care, what benefits and burdens can be attributed to trainees, and how trainees are supervised. Most patients, when informed, allow trainees to play an active role in their care.

IMPAIRED PHYSICIANS Physicians may hesitate to intervene when colleagues impaired by alcohol abuse, drug abuse, or psychiatric or medical illness place patients at risk. However, society relies on physicians to regulate themselves. If colleagues of an impaired physician do not take steps to protect patients, no one else may be in a position to do so.

CONFLICTS FOR TRAINEES Medical students and residents may fear that they will receive poor grades or evaluations if they act on the patient's behalf by disclosing mistakes, avoiding misrepresentation of their role, and reporting impaired colleagues. Discussing such dilemmas with more senior physicians can help trainees check their interpretation of the situation and obtain advice and assistance.

ADDITIONAL ETHICAL ISSUES

MAINTAINING CONFIDENTIALITY Maintaining the confidentiality of medical information respects patients' autonomy and privacy, encourages them to seek treatment and to discuss their problems candidly, and prevents discrimination. Physicians need to guard against inadvertent breaches of confidentiality, as when talking about patients in elevators. Maintaining confidentiality is not an absolute rule. The law may require physicians to override confidentiality in order to protect third parties, for example, reporting to government officials persons with specified infectious conditions, such as tuberculosis and syphilis; persons with gunshot wounds; and victims of elder abuse and domestic violence. Computerized medical records raise additional concerns because breaches of confidentiality may affect many patients.

ALLOCATING RESOURCES JUSTLY Allocation of limited health care resources is problematic. Ideally, allocation decisions should be made as public policy, with physician input. At the bedside, physicians generally should act as patient advocates within constraints set by society, reasonable insurance coverage, and sound practice. *Ad hoc* rationing by the individual physician at the bedside may be inconsistent, discriminatory, and ineffective. In some cases, however, two patients may compete for the same limited resources, such as physician time or a bed in intensive care. When this occurs, physicians should ration their time and resources according to patients' medical needs and the probability of benefit.

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3 DECISION-MAKING IN CLINICAL MEDICINE

Daniel B. Mark

To the medical student who requires 2 h to collect a patient's history and perform a physical examination, and several additional hours to organize them into a coherent presentation, the experienced clinician's ability to reach a diagnosis and decide on a management plan in a fraction of the time seems extraordinary. While medical knowledge and experience play a significant role in the senior clinician's ability to arrive at a differential diagnosis and plan quickly, much of the process involves skill in clinical decision-making. The first goal of this chapter is to provide an introduction to the study of clinical reasoning.

Equally bewildering to the student are the proper use of diagnostic tests and the integration of the results into the clinical assessment. The novice medical practitioner typically uses a "shotgun" approach to testing, hoping to a hit a target without knowing exactly what that target is. The expert, on the other hand, usually has a specific target in mind and efficiently adjusts the testing strategy to it. The second goal of this chapter is to review briefly some of the crucial basic statistical concepts that govern the proper interpretation and use of diagnostic tests; quantitative tools available to assist in clinical decision-making will also be discussed.

CLINICAL DECISION-MAKING

CLINICAL REASONING The most important clinical actions are not procedures or prescriptions but the judgments from which all other aspects of clinical medicine flow. In the modern era of large randomized trials, it is easy to overlook the importance of this elusive mental activity and focus instead on the algorithmic practice guidelines constructed to improve care. One reason for this apparent neglect is that much more research has been done on how doctors *should* make decisions (e.g., using a Bayesian model discussed below) than on how they actually *do*. Thus, much of what we know about clinical reasoning comes from empirical studies of nonmedical problem-solving behavior.

Despite the great technological advances of the twentieth century, uncertainty still plays a pivotal role in all aspects of medical decision-making. We may know that a patient does not have long to live, but we cannot be certain how long. We may prescribe a potent new receptor blocker to reverse the course of a patient's illness, but we cannot be certain that the therapy will do so without side effects. Uncertainty in medical outcomes creates the need for probabilities and other mathematical/statistical tools to help guide decision-making. (These tools are reviewed later in the chapter.)

Uncertainty is compounded by the information overload that characterizes modern medicine. Today's experienced clinician needs close to 2 million pieces of information to practice medicine. Doctors subscribe to an average of 7 journals, representing over 2500 new articles each year. Computers offer the obvious solution both for management of information and for better quantitation and management of the daily uncertainties of medical care. While the technology to computerize medical practice is available, many practical problems remain to be solved before patient information can be standardized and integrated with medical evidence on a single electronic platform.

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The following three examples introduce the subject of clinical reasoning:

- A 46-year-old man presents to his internist with a chief complaint of hemoptysis. The physician knows that the differential diagnosis of hemoptysis includes over 100 different conditions, including cancer and tuberculosis (Chap. 33). The examination begins with some general background questions, and the patient is asked to describe his symptoms and their chronology. By the time the examination is completed, and even before any tests are run, the physician has formulated a working diagnostic hypothesis and planned a series of steps to test it. In an otherwise healthy and nonsmoking patient recovering from a viral bronchitis, the doctor's hypothesis would be that the acute bronchitis is responsible for the small amount of blood-streaked sputum the patient observed. In this case, a chest x-ray and purified protein derivative (PPD) skin test may be sufficient.
- A second 46-year-old patient with the same chief complaint who has a 100-pack-year smoking history, a productive morning cough, and episodes of blood-streaked sputum may generate the principal diagnostic hypothesis of carcinoma of the lung. Consequently, along with the chest x-ray and PPD skin test, the physician refers this patient for bronchoscopy.
- A third 46-year-old patient with hemoptysis who is from a developing country is evaluated with an echocardiogram as well, because the physician thinks she hears a soft diastolic rumble at the apex on cardiac auscultation, suggesting rheumatic mitral stenosis.

These three vignettes illustrate two aspects of expert clinical reasoning: (1) the use of cognitive shortcuts, or *heuristics*, as a way to organize the complex unstructured material that is collected in the clinical evaluation; and (2) the use of diagnostic hypotheses to consolidate the information and indicate appropriate management steps.

THE USE OF COGNITIVE SHORTCUTS Heuristics reduce the complexity of a problem to a manageable level. Psychologists have found that people rely on three basic types of heuristics. For example, when assessing a patient, clinicians often weigh the probability that this patient's clinical features match those of the class of patients with the leading diagnostic hypotheses being considered. In other words, the clinician is searching for the diagnosis for which the patient appears to be a representative example; this cognitive shortcut is called the *representativeness heuristic*. It may take only a few characteristics from the history for an expert clinician using the representativeness heuristic to arrive at a sound diagnostic hypothesis. For example, an elderly patient with new-onset fever, cough productive of copious sputum, unilateral pleuritic chest pain, and dyspnea is readily identified as fitting the pattern for acute pneumonia, probably of bacterial origin. Evidence of focal pulmonary consolidation on the physical examination will increase the clinician's confidence in the diagnosis because it fits the expected pattern of acute bacterial pneumonia. Knowing this allows the experienced clinician to conduct an efficient, directed, and therapeutically productive patient evaluation although there may be little else in the history or physical examination of direct relevance. The inexperienced medical student or resident, who has not yet learned the patterns most prevalent in clinical medicine, must work much harder to achieve the same result and is often at risk of missing the important clinical problem in a sea of compulsively collected but unhelpful data.

However, physicians using the representativeness heuristic can reach erroneous conclusions if they fail to consider the underlying prevalence of two competing diagnoses. Consider a patient with pleuritic chest pain, dyspnea, and a low-grade fever. A clinician might consider acute pneumonia and acute pulmonary embolism to be the two leading diagnostic alternatives. Clinicians using the representativeness heuristic might judge both diagnostic candidates to be equally likely, although to do so would be wrong if pneumonia was much more prevalent in the underlying population. Mistakes may also result from a failure to consider that a pattern based on a small number of prior observations will likely be less reliable than one based on larger samples.

A second commonly used cognitive shortcut, the *availability heuristic*, involves judgments made on the basis of how easily prior similar cases or outcomes can be brought to mind. For example, the experienced clinician may recall 20 elderly patients seen over the past few years who presented with painless dyspnea of acute onset and were found to have acute myocardial infarction. The novice clinician may spend valuable time seeking a pulmonary cause for the symptoms before considering and discovering the cardiac diagnosis. In this situation, the patient's clinical pattern does not fit the expected pattern of acute myocardial infarction, but experience with this atypical presentation, and the ability to recall it, can help direct the physician to the diagnosis.

Errors with the availability heuristic can come from several sources of recall bias. For example, rare catastrophes are likely to be remembered with a clarity and force out of proportion to their value, and recent experience is, of course, easier to recall and therefore more influential on clinical judgments.

The third commonly used cognitive shortcut, the *anchoring heuristic*, involves estimating a probability by starting from a familiar point (the anchor) and adjusting to the new case from there. For example, a clinician may judge the probability of colorectal cancer to be extremely high after an elevated screening carcinoembryonic antigen (CEA) result because the prediction of colorectal cancer is anchored to the test result. Yet, as discussed below, this prediction would be inaccurate if the clinical picture of the patient being tested indicates a low probability of disease (for example, a 30-year-old woman with no risk factors). Anchoring can be a powerful tool for diagnosis but is often used incorrectly (see "Measures of Disease Probability and Bayes' Theorem," below).

DIAGNOSTIC HYPOTHESIS GENERATION Cognitive scientists studying the thought processes of expert clinicians have observed that clinicians group data into packets or "chunks," which are stored in their memories and manipulated to generate diagnostic hypotheses. Because short-term memory can typically hold only 7 to 10 items at a time, the number of packets that can be actively integrated into hypothesis-generating activities is similarly limited. The cognitive shortcuts discussed above play a key role in the generation of diagnostic hypotheses, many of which are discarded as rapidly as they are formed.

A diagnostic hypothesis sets a context for diagnostic steps to follow and provides testable predictions. For example, if the enlarged and quite tender liver felt on physical examination is due to acute hepatitis (the hypothesis), certain specific liver function tests should be markedly elevated (the prediction). If the tests come back normal, the hypothesis may need to be discarded or substantially modified.

One of the factors that makes teaching diagnostic reasoning so difficult is that expert clinicians do not follow a fixed pattern in patient examinations. From the outset, they are generating, refining, and discarding diagnostic hypotheses. The questions they ask in the history are driven by the hypotheses they are working with at the moment. Even the physical examination is driven by specific questions rather than a preordained checklist. While the student is palpating the abdomen of the alcoholic patient, waiting for a finding to strike him, the expert clinician is on a focused search mission. Is the spleen enlarged? How big is the liver? Is it tender? Are there any palpable masses or nodules? Each question focuses the attention of the examiner to the exclusion of all other inputs until answered, allowing the examiner to move on to the next specific question.

Negative findings are often as important as positive ones in establishing and refining diagnostic hypotheses. Chest discomfort that is not provoked or worsened by exertion in an active patient reduces the likelihood that chronic ischemic heart disease is the underlying cause. The absence of a resting tachycardia and thyroid gland enlargement

reduces the likelihood of hyperthyroidism in a patient with paroxysmal atrial fibrillation.

While the representativeness and availability heuristics may play the major roles in shaping early diagnostic hypotheses, the acuity of a patient's illness can also be very influential. For example, clinicians are taught to consider aortic dissection routinely as a possible cause of acute severe chest discomfort along with myocardial infarction, even though the typical history of dissection is different from myocardial infarction and dissection is far less prevalent (Chap. 247). This recommendation is based on the recognition that a relatively rare but catastrophic diagnosis like aortic dissection is very difficult to make unless it is explicitly considered. If the clinician fails to elicit any of the characteristic features of dissection by history and finds equivalent blood pressures in both arms and no pulse deficits, he or she may feel comfortable in discarding the aortic dissection hypothesis. If, however, the chest x-ray shows a widened mediastinum, the hypothesis may be reinstated and a diagnostic test ordered [e.g., thoracic computed tomography (CT) scan, transesophageal echocardiogram] to evaluate it more fully. In noncritical situations, the prevalence of potential alternative diagnoses should play a much more prominent role in diagnostic hypothesis generation. The value of conducting a rapid systematic clinical survey of symptoms and organ systems to avoid missing important but inapparent clues cannot be overstated.

Because the generation and evaluation of appropriate diagnostic hypotheses is a skill that not all clinicians possess to an equal degree, errors in this process can occur, and in the patient with serious acute illness these may lead to tragic consequences. Consider the following hypothetical example. A 45-year-old male patient with a 3-week history of a "flulike" upper respiratory infection (URI) presented to his physician with symptoms of dyspnea and a productive cough. Based on the presenting complaint, the clinician pulled out a "URI Assessment Form" to improve quality and efficiency of care. The physician quickly completed the examination components outlined on this structured form, noting in particular the absence of fever and a clear chest examination. He then prescribed an antibiotic for presumed bronchitis, showed the patient how to breathe into a paper bag to relieve his "hyperventilation," and sent him home with the reassurance that his illness was not serious. After a sleepless night with significant dyspnea unrelieved by rebreathing into a bag, the patient developed nausea and vomiting and collapsed. He was brought into the Emergency Department in cardiac arrest and could not be resuscitated. Autopsy showed a posterior wall myocardial infarction and a fresh thrombus in an atherosclerotic right coronary artery. What went wrong? The clinician decided, even before starting the history, that the patient's complaints were not serious. He therefore felt confident that he could perform an abbreviated and focused examination using the URI assessment protocol rather than considering the full range of possibilities and performing appropriate tests to confirm or refute his initial hypotheses. In particular, by concentrating on the "URI," the clinician failed to elicit the full dyspnea history, which would have suggested a far more serious disorder, and did not even search for other symptoms that could have directed him to the correct diagnosis.

This example illustrates how patients can diverge from textbook symptoms and the potential consequences of being unable to adapt the diagnostic process to real-world challenges. The expert, while recognizing that common things occur commonly, approaches each evaluation on high alert for clues that the initial diagnosis may be wrong. Patients often provide information that "does not fit" with any of the leading diagnostic hypotheses being considered. Distinguishing real clues from false trails can only be achieved by practice and experience. A less experienced clinician who tries to be too efficient (as in the above example) can make serious judgment errors.

MAJOR INFLUENCES ON CLINICAL DECISION-MAKING More than a decade of research on variations in clinician practice patterns has shed much light on forces that shape clinical decisions. The use of heuristic "shortcuts," as detailed above, provides a partial explanation, but several other key factors play an important role in shaping diagnostic hypotheses and management decisions. These factors can be grouped conceptually into three overlapping categories: (1) factors related to physician personal characteristics and practice style, (2) factors related to the practice setting, and (3) economic incentive factors.

Practice Style Factors One of the key roles of the physician in medical care is to serve as the patient's agent to ensure that necessary care is provided at a high level of quality. Factors that influence this role include the physician's knowledge, training, and experience. It is obvious that physicians cannot practice evidence-based medicine if they are unfamiliar with the evidence. As would be expected, specialists generally know the evidence in their field better than do generalists. Surgeons may be more enthusiastic about recommending surgery than medical doctors because their belief in the beneficial effects of surgery is stronger. For the same reason, invasive cardiologists are much more likely to refer chest pain patients for diagnostic catheterization than are noninvasive cardiologists or generalists. The physician beliefs that drive these different practice styles are based on personal experience, recollection, and interpretation of the available medical evidence. For example, heart failure specialists are much more likely than generalists to achieve target angiotensin-converting enzyme (ACE) inhibitor therapy in their heart failure patients because they are more familiar with what the targets are (as defined by large clinical trials), have more familiarity with the specific drugs (including dosages and side effects), and are less likely to overreact to foreseeable problems in therapy such as a rise in creatinine levels or symptomatic hypotension. Other intriguing research has shown a wide distribution of acceptance times of antibiotic therapy for peptic ulcer disease following widespread dissemination of the "evidence" in the medical literature. Some gastroenterologists accepted this new therapy before the evidence was clear (reflecting, perhaps, an aggressive practice style), and some gastroenterologists lagged behind (a conservative practice style, associated in this case with older physicians). As a group, internists lagged several years behind gastroenterologists.

The opinion of influential leaders can also have an important effect on practice patterns. Such influence can occur at both the national level (e.g., expert physicians teaching at national meetings) and the local level (e.g., local educational programs, "curbside consultants"). Opinion leaders do not have to be physicians. When conducting rounds with clinical pharmacists, physicians are less likely to make medication errors and more likely to use target levels of evidence-based therapies.

The patient's welfare is not the only concern that drives clinical decisions. The physician's perception about the risk of a malpractice suit resulting from either an erroneous decision or a bad outcome creates a style of practice referred to as *defensive medicine*. This practice involves using tests and therapies with very small marginal returns to preclude future criticism in the event of an adverse outcome. For example, a 40-year-old woman who presents with a long-standing history of intermittent headache and a new severe headache along with a normal neurologic examination has a very low likelihood of structural intracranial pathology. Performance of a head CT or magnetic resonance imaging (MRI) scan in this situation would constitute defensive medicine. On the other hand, the results of the test could provide reassurance to an anxious patient.

Practice Setting Factors Factors in this category relate to the physical resources available to the physician's practice and the practice environment. *Physician-induced demand* is a term that refers to the repeated observation that physicians have a remarkable ability to accommodate to and employ the medical facilities available to them. A classic early study in this area showed that physicians in Boston had an almost 50% higher hospital admission rate than did physicians in New Haven, despite there being no obvious differences in the health of the cities' inhabitants. The physicians in New Haven were not aware of using fewer hospital beds for their patients, nor were the Boston physicians aware of using less stringent criteria to admit patients.

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This example illustrates how patients can diverge from textbook symptoms and the potential consequences of being unable to adapt the diagnostic process to real-world challenges. The expert, while recognizing that common things occur commonly, approaches each evaluation on high alert for clues that the initial diagnosis may be wrong. Patients often provide information that "does not fit" with any of the leading diagnostic hypotheses being considered. Distinguishing real clues from false trails can only be achieved by practice and experience. A less experienced clinician who tries to be too efficient (as in the above example) can make serious judgment errors.

MAJOR INFLUENCES ON CLINICAL DECISION-MAKING

More than a decade of research on variations in clinician practice patterns has shed much light on forces that shape clinical decisions. The use of heuristic "shortcuts," as detailed above, provides a partial explanation, but several other key factors play an important role in shaping diagnostic hypotheses and management decisions. These factors can be grouped conceptually into three overlapping categories: (1) factors related to physician personal characteristics and practice style, (2) factors related to the practice setting, and (3) economic incentive factors.

Practice Style Factors One of the key roles of the physician in medical care is to serve as the patient's agent to ensure that necessary care is provided at a high level of quality. Factors that influence this role include the physician's knowledge, training, and experience. It is obvious that physicians cannot practice evidence-based medicine if they are unfamiliar with the evidence. As would be expected, specialists generally know the evidence in their field better than do generalists. Surgeons may be more enthusiastic about recommending surgery than medical doctors because their belief in the beneficial effects of surgery is stronger. For the same reason, invasive cardiologists are much more likely to refer chest pain patients for diagnostic catheterization than are noninvasive cardiologists or generalists. The physician beliefs that drive these different practice styles are based on personal experience, recollection, and interpretation of the available medical evidence. For example, heart failure specialists are much more likely than generalists to achieve target angiotensin-converting enzyme (ACE) inhibitor therapy in their heart failure patients because they are more familiar with what the targets are (as defined by large clinical trials), have more familiarity with the specific drugs (including dosages and side effects), and are less likely to overreact to foreseeable problems in therapy such as a rise in creatinine levels or symptomatic hypotension. Other intriguing research has shown a wide distribution of acceptance times of antibiotic therapy for peptic ulcer disease following widespread dissemination of the "evidence" in the medical literature. Some gastroenterologists accepted this new therapy before the evidence was clear (reflecting, perhaps, an aggressive practice style), and some gastroenterologists lagged behind (a conservative practice style, associated in this case with older physicians). As a group, internists lagged several years behind gastroenterologists.

The opinion of influential leaders can also have an important effect on practice patterns. Such influence can occur at both the national level (e.g., expert physicians teaching at national meetings) and the local level (e.g., local educational programs, "curbside consultants"). Opinion leaders do not have to be physicians. When conducting rounds with clinical pharmacists, physicians are less likely to make medication errors and more likely to use target levels of evidence-based therapies.

The patient's welfare is not the only concern that drives clinical decisions. The physician's perception about the risk of a malpractice suit resulting from either an erroneous decision or a bad outcome creates a style of practice referred to as *defensive medicine*. This practice involves using tests and therapies with very small marginal returns to preclude future criticism in the event of an adverse outcome. For example, a 40-year-old woman who presents with a long-standing history of intermittent headache and a new severe headache along with a normal neurologic examination has a very low likelihood of structural intracranial pathology. Performance of a head CT or magnetic resonance imaging (MRI) scan in this situation would constitute defensive medicine. On the other hand, the results of the test could provide reassurance to an anxious patient.

Practice Setting Factors Factors in this category relate to the physical resources available to the physician's practice and the practice environment. *Physician-induced demand* is a term that refers to the repeated observation that physicians have a remarkable ability to accommodate to and employ the medical facilities available to them. A classic early study in this area showed that physicians in Boston had an almost 50% higher hospital admission rate than did physicians in New Haven, despite there being no obvious differences in the health of the cities' inhabitants. The physicians in New Haven were not aware of using fewer hospital beds for their patients, nor were the Boston physicians aware of using less stringent criteria to admit patients.

Other environmental factors that can influence decision-making include the local availability of specialists for consultations and procedures, "high tech" facilities such as angiography suites, a heart surgery program, and MRI machines.

Economic Incentives Economic incentives are closely related to the other two categories of practice-modifying factors. Financial issues can exert both stimulatory and inhibitory influences on clinical practice. In general, physicians are paid on a fee-for-service, capitation, or salary basis (Chap. 4). In fee-for-service, the more the physician does, the more the physician gets paid. The incentive in this case is to do more. When fees are reduced (discounted fee-for-service), doctors tend to increase the number of services billed for. Capitation, in contrast, provides a fixed payment per patient per year, encouraging physicians to take on more patients but to provide each patient with fewer services. Expensive services are more likely to be affected by this type of incentive than inexpensive preventive services. Salary compensation plans pay physicians the same regardless of the amount of clinical work performed. The incentive here is to see fewer patients. Recognizing these powerful shapers of physician behavior, managed care plans have begun to explore combinations of the three reimbursement types with the goal of improving individual physician productivity while restraining their use of expensive tests and therapies.

In summary, expert clinical decision-making can be appreciated as a complex interplay between cognitive devices used to simplify large amounts of complex information interacting with physician biases reflecting education, training, and experience, all of which are shaped by powerful, sometimes perverse, external forces. In the next section, we will review a set of statistical tools and concepts that can assist in making clinical decisions under uncertainty.

QUANTITATIVE METHODS TO AID CLINICAL DECISION-MAKING

The process of medical decision-making can be divided into two parts: (1) defining the available courses of action and estimating the likely outcomes with each, and (2) assessing the desirability of the outcomes. The former task involves integrating key information about the patient along with relevant evidence from the medical literature to create the structure of a decision problem. The remainder of this chapter will present some quantitative tools to assist the clinician in these activities. These tools can be divided into those that assist the clinician in making better outcome predictions, which are then used to make decisions, and those that support the decision process directly. While these tools are not yet used routinely in daily clinical practice, the computerization of medicine is creating the required substrate for their future widespread dissemination.

QUANTITATIVE MEDICAL PREDICTIONS **Diagnostic Testing** The purpose of performing a test on a patient is to reduce uncertainty about the patient's diagnosis or prognosis and to aid the clinician in making management decisions. Although diagnostic tests are commonly thought of as laboratory tests (e.g., measurement of serum amylase level) or procedures (e.g., colonoscopy or bronchoscopy), any technology that changes our understanding of the patient's problem qualifies as a diagnostic test. Thus, even the history and physical examination can be considered a form of diagnostic test. In clinical medicine, it is common to reduce the results of a test to a dichotomous outcome, such as positive or negative, normal or abnormal. In many cases, this simplification results in the waste of useful information. However, such simplification makes it easier to demonstrate some of the quantitative ways in which test data can be used.

To characterize the accuracy of diagnostic tests, four terms are routinely used (Table 3-1). The *true-positive rate*, i.e., the sensitivity, provides a measure of how well the test correctly identifies patients with disease. The *false-negative rate* is calculated as (1 − sensitivity). The *true-negative rate*, i.e., the specificity, reflects how well the test correctly identifies patients without disease. The *false-positive rate* is (1 − specificity). A perfect test would have a sensitivity of 100% and a specificity of 100% and would completely separate patients with disease from those without it.

Table 3-1 Measures of Diagnostic Test Accuracy

	Disease Status	
Test Result	Present	Absent
Positive	True-positive (*TP*)	False-positive (*FP*)
Negative	False-negative (*FN*)	True-negative (*TN*)

IDENTIFICATION OF PATIENTS WITH DISEASE

True-positive rate (sensitivity) = $TP/(TP + FN)$
False-negative rate = $FN/(TP + FN)$
True-positive rate = 1 − false-negative rate

IDENTIFICATION OF PATIENTS WITHOUT DISEASE

True-negative rate (specificity) = $TN/(TN + FP)$
False-positive rate = $FP/(TN + FP)$
True-negative rate = 1 − false-positive rate

Calculating sensitivity and specificity require selection of a cut-point value for the test to separate "normal" from "diseased" subjects. As the cutpoint is moved to improve sensitivity, specificity typically falls and vice versa. This dynamic tradeoff between more accurate identification of subjects with versus those without disease is often displayed graphically as a receiver operating characteristic (ROC) curve. An ROC curve plots sensitivity (y-axis) versus 1 − specificity (x-axis). Each point on the curve represents a potential cutpoint with an associated sensitivity and specificity value. The area under the ROC curve is often used as a quantitative measure of the information content of a test. Values range from 0.5 (no diagnostic information at all, test is equivalent to flipping a coin) to 1.0 (perfect test).

In the diagnostic testing literature, ROC areas are often used to compare alternative tests. The test with the highest area (i.e., closest to 1.0) is presumed to be the most accurate. However, ROC curves are not a panacea for evaluation of diagnostic test utility. Like Bayes' theorem, they are typically focused on only one possible test parameter (e.g., ST segment response in a treadmill exercise test) to the exclusion of other potentially relevant data. In addition, ROC area comparisons do not simulate the way test information is actually used in clinical practice. Finally, biases in the underlying population used to generate the ROC curves (e.g., related to an unrepresentative test sample) can bias the ROC area and the validity of a comparison among tests.

Measures of Disease Probability and Bayes' Theorem Unfortunately, there are no perfect tests; after every test is completed the true disease state of the patient remains uncertain. Quantitating this residual uncertainty can be done with Bayes' theorem. This theorem provides a simple mathematical way to calculate the posttest probability of disease from three parameters: the pretest probability of disease, the test sensitivity, and the test specificity (Table 3-2). The pretest probability is a quantitative expression of the confidence in a diagnosis before the test is performed. In the absence of more relevant information it is usually estimated from the prevalence of the disease in the underlying population. For some common conditions, such as coronary artery disease (CAD), nomograms and statistical models have been created to generate better estimates of pretest probability from elements of the history and physical examination. The posttest probability, then, is a revised statement of the confidence in the diagnosis, taking into account both what was known before and after the test.

To understand how Bayes' theorem creates this revised confidence statement, it is useful to examine a nomogram version of Bayes' theorem that uses the same three parameters to predict the posttest probability of disease (Fig. 3-1). In this nomogram, the accuracy of the diagnostic test in question is summarized by the likelihood ratio for a

Table 3-2 Measures of Disease Probability

Pretest probability of disease = probability of disease before test is done; may use population prevalence of disease or more patient-specific data to generate this probability estimate.

Posttest probability of disease = probability of disease accounting for both pretest probability and test results; also called predictive value of the test.

Bayes' theorem

Computational version:

$$\text{Posttest probability} = \frac{\text{Pretest probability} \times \text{test sensitivity}}{\text{Pretest probability} \times \text{test sensitivity} + (1 - \text{disease prevalence}) \times \text{test false-positive rate}}$$

Example [with a pretest probability of 0.50 and a "positive" diagnostic test result (test sensitivity = 0.90, test specificity = 0.90)]:

$$\text{Posttest probability} = \frac{(0.50)(0.90)}{(0.50)(0.90) + (0.50)(0.10)} = 0.90$$

positive test, which is the ratio of the true-positive rate to the false-positive rate [or sensitivity/(1 − specificity)]. For example, a test with a sensitivity of 0.90 and a specificity of 0.90 has a likelihood ratio of 0.90/(1 − 0.90), or 9. Thus, for this hypothetical test, a "positive" result is 9 times more likely in a patient with the disease than in a patient without it. The more accurate the test, the higher the likelihood ratio. However, if sensitivity is excellent but specificity is less so, the likelihood ratio will be substantially reduced (e.g., with a 90% sensitivity but a 60% specificity, the likelihood ratio is 2.25). Most tests in medicine have likelihood ratios for a positive result between 1.5 and 20.

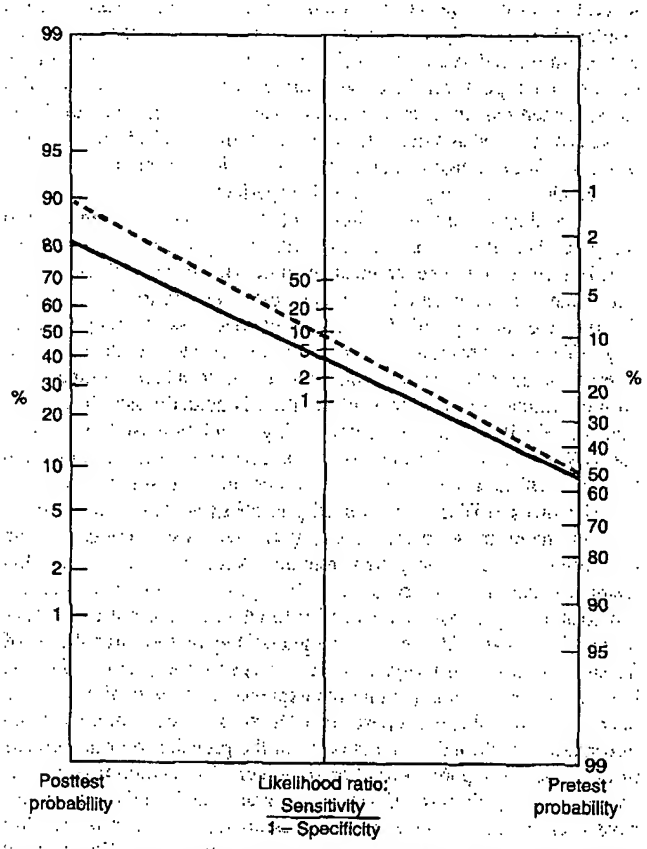

FIGURE 3-1 Nomogram version of Bayes' theorem used to predict the posttest probability of disease (left-hand scale) using the pretest probability of disease (right-hand scale) and the likelihood ratio for a positive test (middle scale). The likelihood ratio is calculated as the sensitivity/(1 − specificity). To use, place a straight edge connecting the pretest probability and the likelihood ratio, and read off the posttest probability. This figure illustrates the value of a positive exercise treadmill test (likelihood ratio 4) and a positive exercise thallium SPECT study (likelihood ratio 9) in the patient with a pretest probability of coronary artery disease of 50%. Treadmill results shown in solid line; thallium results in dashed line. *(Adapted from Fagan TJ: N Engl J Med 293:257, 1975.)*

Consider two tests commonly used in the diagnosis of CAD, an exercise treadmill and an exercise thallium-201 single photon emission CT (SPECT) test (Chap. 244). Meta-analysis has shown the treadmill to have an average sensitivity of 66% and an average specificity of 84%, yielding a likelihood ratio of 4.1 [0.66/(1 − 0.84)]. If we use this test on a patient with a pretest probability of CAD of 10%, the posttest probability of disease following a positive result rises only to about 30%. If a patient with a pretest probability of CAD of 80% has a positive test result, the posttest probability of disease is about 95%.

The exercise thallium SPECT test is a more accurate test for the diagnosis of CAD. For our purposes, assume that it has both a sensitivity and specificity of 90%, yielding a likelihood ratio of 9.0 [0.90/(1 − 0.90)]. If we again test our low pretest probability patient and he has a positive test, using Fig. 3-1 we can demonstrate that the posttest probability of CAD rises from 10 to 50%. However, from a decision-making point of view, the more accurate test has not been able to improve diagnostic confidence enough to change management. In fact, the test has moved us from being fairly certain that the patient did not have CAD to being completely undecided (a 50:50 chance of disease). In a patient with a pretest probability of 80%, using the more accurate thallium SPECT test raises the posttest probability to 97% (compared with 95% for the exercise treadmill). Again, the more accurate test does not provide enough improvement in posttest confidence to alter management, and neither test has improved much upon what was known from clinical data alone.

If the pretest probability is low (e.g., ≤20%), even a positive result on a very accurate test will not move the posttest probability to a range high enough to rule in disease (e.g., ≥80%). Conversely, with a high pretest probability, a negative test will not adequately rule out disease. Thus, the largest gain in diagnostic confidence from a test occurs when the clinician is most uncertain before performing it (e.g., pretest probability between 30 and 70%). For example, if a patient has a pretest probability for CAD of 50%, a positive exercise treadmill test will move the posttest probability to 80% and a positive exercise thallium SPECT test will move it to 90% (Fig. 3-1).

Bayes' theorem, as presented above, employs a number of important simplifications that should be considered. First, few tests have only two useful outcomes, positive or negative, and many tests provide numerous pieces of data about the patient. Even if these can be integrated into a summary result, multiple levels of useful information may be present (e.g., strongly positive, positive, indeterminate, negative, strongly negative). While Bayes' theorem can be adapted to this more detailed test result format, it is computationally complex to do so. Second, Bayes' theorem assumes that the information from the test is completely unique and nonoverlapping with information used to estimate the pretest probability. This independence assumption, however, is often wrong. In many cases, test results are correlated with patient characteristics. For example, the findings of cardiomegaly and pulmonary edema on chest x-ray are correlated with the historic features of heart failure and with the physical findings of a displaced left ventricular apical impulse, an S_3 gallop, and rales. The unique predictive information contributed by the test in this case (the chest x-ray) is only a fraction of its total information because much had already been learned about the probability of heart failure before the test was done.

Finally, it has long been thought that sensitivity and specificity are prevalence-independent parameters of test accuracy, and many texts still make this assertion. This statistically useful assumption, however, is clinically wrong. For example, a treadmill exercise test has a sensitivity in a population of patients with one-vessel CAD of around 30%, whereas the sensitivity in severe three-vessel CAD approaches

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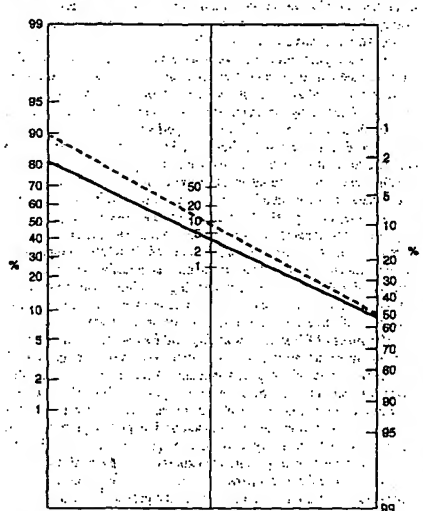

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Statistical Prediction Models

Bayes' theorem, as presented above, deals with a clinical prediction problem that is unrealistically simple relative to most problems a clinician faces. Prediction models, based on multivariable statistical models, can handle much more complex problems and substantially enhance predictive accuracy for specific situations. Their particular advantage is the ability to take into account many overlapping pieces of information and assign a relative weight to each based on its unique contribution to the prediction in question. For example, a logistic regression model to predict the probability of CAD takes into account all of the relevant independent factors from the clinical examination and diagnostic testing instead of the small handful of data that clinicians can manage in their heads or, with Bayes' theorem. However, despite this strength, the models are too complex computationally to use without a calculator or computer (although this limit may be overcome when medicine is practiced from a fully computerized platform.) To date, only a handful of prediction models have been developed and properly validated. The importance of independent validation in a population separate from the one used to develop the model cannot be overstated. Unfortunately, most published models have not been properly validated, making their utility in clinical practice uncertain at best.

When statistical models have been compared directly with expert clinicians, they have been found to be more consistent, as would be expected, but not significantly more accurate. Their biggest promise, then, would seem to be to make less-experienced clinicians more accurate predictors of outcome.

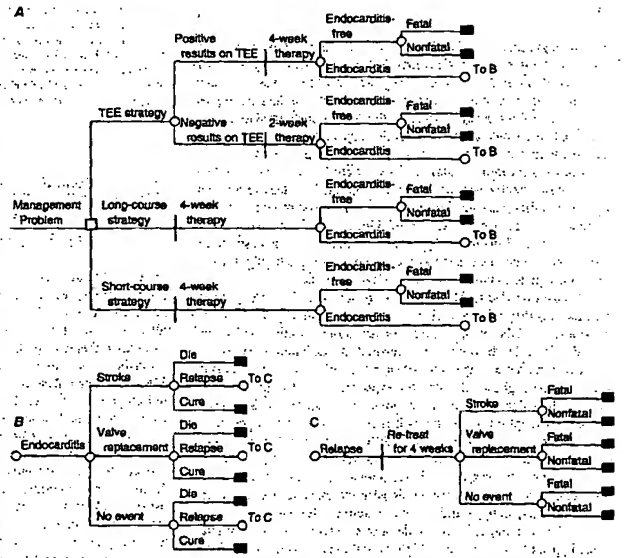

FIGURE 3-2 Decision model used to evaluate strategies for management of the risk of infective endocarditis after catheter-associated *Staphylococcus aureus* bacteremia. The square node indicates a decision between possible management strategies, round nodes represent chance events, and rectangular (or terminal) nodes indicate the outcomes of interest. All nonterminal chance nodes in the main tree (structure *A*) enter substructure *B*. All nonterminal chance nodes in substructure *B* enter substructure *C*. TEE, transesophageal echocardiography. *(From Roizen et al.)*

DECISION SUPPORT TOOLS

DECISION SUPPORT SYSTEMS: Over the past 30 years, many attempts have been made to develop computer systems to help clinicians make decisions and manage patients. Conceptually, computers offer a very attractive way to handle the vast information load that today's physicians face. The computer can help by making accurate predictions of outcome, simulating the whole decision process, providing algorithmic guidance. Computer-based predictions using Bayesian or statistical regression models inform a clinical decision but do not actually reach a "conclusion" or "recommendation." Artificial intelligence systems attempt to simulate or replace human reasoning with a computer-based analogue. To date, such approaches have achieved only limited success. Reminder or protocol-directed systems do not make predictions but use existing algorithms, such as practice guidelines, to guide clinical practice. In general, however, decision support systems have shown little impact on practice. Reminder systems, although not yet in widespread use, have shown the most promise, particularly in correcting drug dosing and in promoting guideline adherence. The full potential of these approaches will only be achieved when computers are fully integrated into medical practice.

DECISION ANALYSIS Compared with the methods discussed above, decision analysis represents a completely different approach to decision support. Its principal application is in decision problems that are complex and involve a substantial risk, a high degree of uncertainty in some key area, or an idiosyncratic feature that does not "fit" the available evidence. Three general steps are involved. First, the decision problem must be clearly defined. Second, the elements of the decision must be made explicit. This involves specifying the alternatives being considered, their relevant outcomes, the probabilities attached to each outcome, and the relative desirability (called "utility") of each outcome. Cost can also be assigned to each branch of the decision tree, allowing calculation of cost-effectiveness (Chap. 4).

An example of a decision tree used to evaluate strategies for management of the risk of infective endocarditis after catheter-associated *Staphylococcus aureus* bacteremia is shown in Fig. 3-2. Approximately 35,000 cases of *S. aureus* bacteremia occur each year in the United States. The development of complicating endocarditis, which occurs in about 6% of cases, is associated with high morbidity (31% mortality, 21% stroke rate) and medical costs. The three choices for management of the bacteremia are (1) transesophageal echocardiography (TEE), (2) a 4-week course of intravenous antibiotics (long-course), or (3) a 2-week course of intravenous antibiotics (short-course). In the TEE strategy, a 4-week course of antibiotics is given if endocarditis is evident and a 2-week course is given if it is not. With

each strategy, there is a risk that the patient will develop endocarditis with or without major complications. In this analysis, the longest quality-adjusted survival (5.47 quality-adjusted life-years) was associated with the 4-week antibiotic course strategy, which also had the highest costs ($14,136 per patient), whereas the lowest costs ($9830 per patient) and worst outcomes (5.42 quality-adjusted life-years) were associated with the 2-week antibiotic course strategy. From a clinical point of view (ignoring costs), the 4-week antibiotic course was best. From a cost-effectiveness point of view, the TEE strategy (5.46 quality-adjusted life-years and $10,051 per patient costs) provided the best balance of added benefits and costs. Thus, decision analysis can be extremely helpful in clarifying tradeoffs in outcomes and costs in difficult management areas such as the above where it is highly unlikely that an adequate randomized trial will ever be done.

The data needed to fill in a decision tree (Fig. 3-2) are typically cobbled together from a variety of sources, including the literature (randomized trials, meta-analyses, observational studies) and expert opinion. Once the decision tree is finished, the decision is "analyzed" by calculating the average value of each limb of the tree. The decision arm with the highest net value (or expected utility) is the preferred choice. The value of this exercise, however, is not so much in developing a prescription for action as it is in exploring the key elements and pressure points of a complex or difficult decision. The process of building the decision tree forces the analyst to be explicit about the choices being considered and all their relevant outcomes. Areas of high uncertainty are readily identified. Sensitivity analyses are an integral part of decision analysis and involve systematically varying the value of each key parameter in the model alone (one-way sensitivity analysis,) in pairs (two-way), or in higher combinations (multivariable) to assess the impact on choice of preferred management strategy. In the above example, varying the incidence of endocarditis resulting from *S. aureus* bacteremia from 3% to over 50% had no impact on the choice of TEE as the preferred strategy.

User friendly personal computer–based software packages now make the creation and analysis of decision trees much more straightforward than in the past. However, the process is still too cumbersome and time-consuming to be used on a routine basis. When medicine is practiced from a fully computerized platform, a library of prestructured decision trees with user modifiable values can be made available to support practitioners working with individual patients.

CONCLUSIONS

In this era of evidence-based medicine, it is tempting to think that all the difficult decisions practitioners face have been or soon will be solved and digested into practice guidelines and computerized reminders. For the foreseeable future, however, such is not the case. Meta-analyses cannot generate evidence where there are no adequate randomized trials, and most of what clinicians face will never be thoroughly tested in a randomized trial. Excellent clinical reasoning skills and experience supplemented by well-designed quantitative tools and a keen appreciation for individual patient preferences will continue to be of paramount importance in the professional life of medical practitioners for years to come.

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ECONOMIC ISSUES IN CLINICAL MEDICINE

The United States has the distinction of having some of the best medical care of any technologically advanced country. We have many of the best hospitals and doctors in the world. The research pipeline is full of significant new therapeutic advances, with revolutionary genetic-based therapies perhaps only a decade away. Our citizens largely subscribe to the principle that excellent medical care should be available to all, regardless of ability to pay. Yet we also have over 43 million people (most of them employed and earning minimal wages) without any health insurance and many more who are inadequately insured. Since the collapse of the Clinton health care reform efforts in 1994, U.S. health policy has been directed by marketplace forces that have created powerful and sometimes perverse incentives in medicine: Health insurance companies that use every available means to avoid insuring sick people; "managed care" programs that really only manage costs; doctors who are provided incentives to provide less medical care; and pharmaceutical companies that develop powerful and expensive new drugs priced beyond the reach of many of the elderly and chronically ill who need them most.

Facing such powerful and chaotic forces, physicians tend to focus narrowly on what they are most comfortable with, taking care of individual patients and conducting academic investigations. Many doctors consider economics too arcane for them to grasp and therefore do not even try. Consequently, when presented with economic arguments and evidence they are often unable to discriminate the legitimate from the fallacious. More importantly, they are ill equipped to defend their patients' interests in the crucible of cost containment that characterizes the modern managed care era.

This chapter has two goals: first, to provide a brief introduction to some of the larger economic forces that shape modern medical practices, and second, to introduce the economic tools that are used for assessing the value of medical practices, including cost effectiveness analysis.

HEALTH CARE SPENDING AND FINANCING

HOW MUCH IS SPENT ON HEALTH CARE? In 1997, the United States spent $1.1 trillion on its health care system, representing 13.5% of the gross domestic product (GDP) (a crude measure of national income). Most of this ($969 billion) was spent on personal health care: 34% went to hospitals, 20% to physicians, 7% to nursing homes, and 8% to outpatient pharmaceuticals. In comparison, Canada and Western European countries spend a substantially smaller portion (6 to 10%) of their national income on health care but their citizens appear to be equally healthy, at least by crude metrics such as life expectancy and infant mortality rates. Economists and politicians have for years used such data to argue that the United States spends too much on health care. The issue of how much to spend is an inherently political one, however, and the discipline of economics has little to say about it.

WHO PAYS FOR HEALTH CARE? Two major factors are continually driving up the costs of medical care: introduction into medical practice of new medical technologies (drugs, devices, procedures) that have a high price tag, and the aging of the U.S. population

sincere concern, the willingness to take the time to explain all aspects of the illness, and a nonjudgmental attitude when dealing with patients whose cultures, lifestyles, attitudes, and values differ from those of the physician are just a few of the characteristics of the humane physician. Every physician will, at times, be challenged by patients who evoke strongly negative (or strongly positive) emotional responses. Physicians should be alert to their own reactions to such patients and situations and should consciously monitor and control their behavior so that the patients' best interests remain the principal motivation for their actions at all times.

An important aspect of patient care involves an appreciation of the "quality of life," a subjective assessment of what each patient values most. Such an assessment requires detailed, sometimes intimate knowledge of the patient, which can usually be obtained only through deliberate, unhurried, and often repeated conversations. It is in these situations that the time constraints of a managed care setting may prove problematic.

The famous statement of Dr. Francis Peabody is even more relevant today than when delivered more than three-quarters of a century ago:

The significance of the intimate personal relationship between physician and patient cannot be too strongly emphasized, for in an extraordinarily large number of cases both the diagnosis and treatment are directly dependent on it. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.

CLINICAL SKILLS **History Taking** The written history of an illness should embody all the facts of medical significance in the life of the patient. Recent events should be given the most attention. The patient should, at some point, have the opportunity to tell his or her own story of the illness without frequent interruption and, when appropriate, receive expressions of interest, encouragement, and empathy from the physician. The physician must be alert to the possibility that any event related by the patient, however trivial or apparently remote, may be the key to the solution of the medical problem.

An informative history is more than an orderly listing of symptoms; something is always gained by listening to patients and noting the way in which they describe their symptoms. Inflections of voice, facial expression, gestures, and attitude may reveal important clues to the meaning of the symptoms to the patient. Taking history often involves much data gathering. Patients vary in their medical sophistication and ability to recall facts. Medical history should therefore be corroborated whenever possible. The family and social history can also provide important insights into the types of diseases that should be considered. In listening to the history, the physician discovers not only something about the disease but also something about the patient. The process of history taking provides an opportunity to observe the patient's behavior and to watch for features to be pursued more thoroughly during the physical examination.

The very act of eliciting the history provides the physician with the opportunity to establish or enhance the unique bond that is the basis for the ideal patient-physician relationship. It is helpful to develop an appreciation of the patient's perception of the illness, the patient's expectations of the physician and the medical care system, and the financial and social implications of the illness to the patient. The confidentiality of the patient-physician relationship should be emphasized, and the patient should be given the opportunity to identify any aspects of the history that should not be disclosed.

Physical Examination Physical signs are objective indications of disease whose significance is enhanced when they confirm a functional or structural change already suggested by the patient's history. At times, however, the physical signs may be the only evidence of disease.

The physical examination should be performed methodically and thoroughly, with consideration for the patient's comfort and modesty. Although attention is often directed by the history to the diseased organ or part of the body, the examination of a new patient must extend from head to toe in an objective search for abnormalities. Unless the physical examination is systematic, important segments may be omitted. The results of the examination, like the details of the history, should be recorded at the time they are elicited, not hours later when they are subject to the distortions of memory. Skill in physical diagnosis is acquired with experience, but it is not merely technique that determines success in eliciting signs. The detection of a few scattered petechiae, a faint diastolic murmur, or a small mass in the abdomen is not a question of keener eyes and ears or more sensitive fingers but of a mind alert to these findings. Since physical findings are subject to changes, the physical examination should be repeated as frequently as the clinical situation warrants.

Laboratory Tests The availability of a wide array of laboratory tests has increased our reliance on these studies for the solution of clinical problems. The accumulation of laboratory data does not relieve the physician from the responsibility of careful observation, examination, and study of the patient. It is also essential to bear in mind the limitations of such tests. By virtue of their impersonal quality, complexity, and apparent precision, they often gain an aura of authority regardless of the fallibility of the tests themselves, the instruments used in the tests, and the individuals performing or interpreting them. Physicians must weigh the expense involved in the laboratory procedures they order relative to the value of the information they are likely to provide.

Single laboratory tests are rarely ordered. Rather, they are generally obtained as "batteries" of multiple tests, which are often useful. For example, abnormalities of hepatic function may provide the clue to such nonspecific symptoms as generalized weakness and increased fatigability, suggesting the diagnosis of chronic liver disease. Sometimes a single abnormality, such as an elevated serum calcium level, points to particular diseases, such as hyperparathyroidism or underlying malignancy.

The thoughtful use of screening tests should not be confused with indiscriminate laboratory testing. The use of screening tests is based on the fact that a group of laboratory determinations can be carried out conveniently on a single specimen of blood at relatively low cost. Screening tests are most useful when they are directed towards common diseases or disorders in which the result directs other useful tests or interventions that would otherwise be costly to perform. Biochemical measurements, together with simple laboratory examinations such as blood count, urinalysis, and sedimentation rate, often provide the major clue to the presence of a pathologic process. At the same time, the physician must learn to evaluate occasional abnormalities among the screening tests that may not necessarily connote significant disease. An in-depth workup following a report of an isolated laboratory abnormality in a person who is otherwise well is almost invariably wasteful and unproductive. Among the more than 40 tests that are routinely performed on patients, one or two are often slightly abnormal. If there is no suspicion of an underlying illness, these tests are ordinarily repeated to ensure that the abnormality does not represent a laboratory error. If an abnormality is confirmed, it is important to consider its potential significance in the context of the patient's condition and other test results.

Imaging Techniques The availability of ultrasonography, a variety of scans that employ isotopes to visualize organs heretofore inaccessible, computed tomography, and magnetic resonance imaging has opened new diagnostic vistas and has benefited patients because these new techniques have largely supplanted more invasive ones. While the enthusiasm for noninvasive technology is understandable, the expense entailed in performing these tests is often substantial and should be considered when assessing the potential benefits of the information provided.

PRINCIPLES OF PATIENT CARE **Medical Decision-Making** Both during and in particular after the physician has taken the history, performed the physical examination, and reviewed the laboratory and imaging data, the challenging process of the differential diagnosis and medical decision-making begins. Formulating a differ-

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PRINCIPLES OF PATIENT CARE **Medical Decision-Making** Both during and in particular after the physician has taken the history, performed the physical examination, and reviewed the laboratory and imaging data, the challenging process of the differential diagnosis and medical decision-making begins. Formulating a differential diagnosis requires not only a broad knowledge base but also the ability to assess the relative probabilities of various diseases and to understand the significance of missing diagnoses that may be less likely. Arriving at a diagnosis requires the application of the scientific method. Hypotheses are formed, data are collected, and objective conclusions are reached concerning whether to accept or reject a particular diagnosis. Analysis of the differential diagnosis is an iterative process. As new information or test results are acquired, the group of disease processes being considered can be contracted or expanded appropriately. Medical decision-making occurs throughout the diagnostic and treatment process. It involves the ordering of additional tests, requests for consults, and decisions regarding prognosis and treatment. This process *requires an in-depth understanding of the natural history* and pathophysiology of disease, explaining why these features are strongly emphasized in this textbook. As described below, medical decision-making should be evidence-based, thereby ensuring that patients derive the full benefit of the scientific knowledge available to physicians.

Evidence-Based Medicine Sackett has defined evidence-based medicine as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." Rigorously obtained evidence is contrasted with anecdotal experience, which is often biased. Even the most experienced physicians can be influenced by recent experiences with selected patients, unless they are attuned to the importance of using larger, more objective studies for making decisions. The prospectively designed, double-blind, randomized clinical trial represents the "gold standard" for providing evidence regarding therapeutic decisions, but it is not the only source. Valuable evidence about the natural history of disease and prognosis can come from prospective cohort studies and analytic surveys. Persuasive evidence on the accuracy of diagnostic tests can be derived from cross-sectional studies of patients in whom a specific disorder is suspected. Evidence is strengthened immensely when it has been confirmed by multiple investigations, which can be compared with one another and presented in a meta-analysis or systemic overview.

In failing to apply the best and most current evidence, the physician places the patient at unnecessary risk. However, a knowledge of or rapid access to the best available evidence is not sufficient for optimal care. The physician must know whether the evidence is relevant to the patient in question and, when it is, the consequences of applying it in any particular situation. The skills and judgment required to apply sound evidence represent an increasing challenge. Indeed, one might redefine a "good doctor" as one who uses the ever-growing body of rigorously obtained evidence (the science of medicine) in a sensible, compassionate manner (the art of medicine).

While an understanding of biologic and physiologic mechanisms forms the basis of contemporary medicine, when a therapeutic modality is selected, the highest priority must often be placed on improving *clinical outcome* rather than interrupting what is believed to be the underlying process. For example, for decades patients who had suffered myocardial infarction were treated intuitively with drugs that suppress frequent ventricular extrasystoles, since these were believed to be harbingers of ventricular fibrillation and sudden death. Clinical trials, however, have provided firm evidence that the antiarrhythmic agents actually increase the risk of death in such patients. This finding suggests that the extrasystoles are *markers of high risk rather than the cause* of fatal events.

Practice Guidelines Physicians are faced with a large, increasing, and often bewildering body of evidence pointing to potentially useful diagnostic techniques and therapeutic choices. The intelligent and cost-effective practice of medicine consists of making selections most appropriate to a particular patient and clinical situation. Professional organizations and government agencies are developing formal clinical practice guidelines in an effort to aid physicians and other caregivers in this endeavor. When guidelines are current and properly applied, they can provide a useful framework for managing patients with particular diagnoses or symptoms. They can protect patients—particularly those with inadequate health care benefits—from receiving substandard care. Guidelines can also protect conscientious caregivers from inappropriate charges of malpractice and society from the excessive costs associated with the overuse of medical resources. On the other hand, clinical guidelines tend to oversimplify the complexities of medicine. Different groups with differing perspectives may develop divergent recommendations regarding issues as basic as the need for periodic sigmoidoscopy in middle-aged persons. Furthermore, guidelines do not—and cannot be expected to—take into account the uniqueness of each individual and of his or her illness. The challenge for the physician is to integrate into clinical practice the useful recommendations offered by the experts who prepare clinical practice guidelines without accepting them blindly or being inappropriately constrained by them.

Assessing the Outcome of Treatment Clinicians generally use *objective* and readily measurable parameters to judge the outcome of a therapeutic intervention. For example, findings on physical or laboratory examination—such as the level of blood pressure, the patency of a coronary artery on an angiogram, or the size of a mass on a radiologic examination—can provide information of critical importance. However, patients usually seek medical attention for *subjective reasons; they wish to obtain relief from pain, to preserve or regain* function, and to enjoy life. The components of a patient's health status or quality of life can include bodily comfort, capacity for physical activity, personal and professional function, sexual function, cognitive function, and overall perception of health. Each of these important areas can be assessed by means of structured interviews or specially designed questionnaires. Such assessments also provide useful parameters by which the physician can judge the patient's subjective view of his or her disability and the response to treatment, particularly in chronic illness. The practice of medicine requires consideration and integration of both objective and subjective outcomes.

Care of the Elderly Over the next several decades, the practice of medicine will be greatly influenced by the health care needs of the growing elderly population. In the United States the population over age 65 will almost triple over the next 30 years. It is essential that we understand and appreciate the physiologic processes associated with aging; the different responses of the elderly to common diseases; and disorders that occur commonly with aging, such as depression, dementia, frailty, urinary incontinence, and fractures. The elderly have more adverse reactions to drugs, in large part due to altered pharmacokinetics and pharmacodynamics. Commonly used medications such as digoxin and aminoglycosides have prolonged half-lives in the elderly, and tissues such as the central nervous system are more sensitive to certain drugs, such as the benzodiazepines and narcotics. The large number of drugs used by the elderly increases the risk of unwanted interactions, especially when care is provided by several physicians in an uncoordinated manner.

Diseases in Women versus Men In the past, many epidemiologic studies and clinical trials focused on men. It is now appreciated that there are significant gender differences in diseases that afflict both men and women. Mortality rates are substantially higher in women than in men under the age of 50 suffering acute myocardial infarction. Hypertension is more prevalent in African-American women than in their male counterparts (and in African-American than in white males); osteoporosis is more common in women, reflecting the menopausal loss of estrogen; diseases involving the immune system, such as lupus erythematosus, multiple sclerosis, and primary biliary cirrhosis, occur more frequently in women; and the average life expectancy of women is greater than that of men. Recently, considerable attention has been paid to women's health issues, a subject that regrettably did not receive sufficient attention in the past. Ongoing study should enhance our understanding of the mechanisms of gender differences in the course and outcome of certain diseases.

Iatrogenic Disorders In an *iatrogenic disorder*, the deleterious effects of a therapeutic or diagnostic maneuver cause pathology in-

(e.g., the *Candida* aspartyl proteinase) have been implicated in fungal invasion of host tissues.

If pathogens are effectively to invade host tissues (particularly the blood), they must avoid the major host defenses represented by complement and phagocytic cells. Bacteria most often avoid these defenses through their cell surface polysaccharides—either capsular polysaccharides or long O-side-chain antigens characteristic of the smooth LPS of gram-negative bacteria. These molecules can prevent the activation and/or deposition of complement opsonins or limit the access of phagocytic cells with receptors for complement opsonins to these molecules when they are deposited on the bacterial surface below the capsular layer. Another potential mechanism of microbial virulence is the ability of some organisms to present the capsule as an apparent self antigen through molecular mimicry. For example, the polysialic acid capsule of group B *N. meningitidis* is chemically identical to an oligosaccharide found on human brain cells.

Immunochemical studies of capsular polysaccharides have led to an appreciation of the tremendous chemical diversity that can result from the linking of a few monosaccharides. For example, three hexoses can link up in more than 300 different, potentially serologically distinct ways, while three amino acids have only six possible peptide combinations. Capsular polysaccharides have been used as effective vaccines against meningococcal meningitis as well as against pneumococcal and *H. influenzae* infections and may prove to be of value as vaccines against any organisms that express a nontoxic, immunogenic capsular polysaccharide. In addition, most encapsulated pathogens become virtually avirulent when capsule production is interrupted by genetic manipulation; this observation emphasizes the importance of this structure in pathogenesis.

HOST RESPONSE The inflammatory response of the host is critical for interruption and resolution of the infectious process but also is often responsible for the signs and symptoms of disease. Infection promotes a complex series of host responses involving the complement, kinin, and coagulation pathways. The production of cytokines such as IL-1, TNF-α, and other factors regulated in part by the NF-κB transcription factor leads to fever, muscle proteolysis, and other effects, as noted above. An inability to kill or contain the microbe usually results in further damage due to the progression of inflammation and infection. For example, in many chronic infections, degranulation of host inflammatory cells can lead to release of host proteases, elastases, histamines, and other toxic substances that can degrade host tissues. Chronic inflammation in any tissue can lead to the destruction of that tissue and to clinical disease associated with loss of organ function, such as sterility from pelvic inflammatory disease caused by chronic infection with *N. gonorrhoeae*.

The nature of the host response elicited by the pathogen often determines the pathology of a particular infection. Local inflammation produces local tissue damage, while systemic inflammation, such as that seen during sepsis, can result in the signs and symptoms of septic shock. The severity of septic shock is associated with the degree of production of host effectors. Disease due to intracellular parasitism results from the formation of granulomas, wherein the host attempts to wall off the parasite inside a fibrotic lesion surrounded by fused epithelial cells that make up so-called multinucleated giant cells. A number of pathogens, particularly anaerobic bacteria, staphylococci, and streptococci, provoke the formation of an abscess, probably because of the presence of zwitterionic surface polysaccharides such as the capsular polysaccharide of *Bacteroides fragilis*. The outcome of an infection depends on the balance between an effective host response that eliminates a pathogen and an excessive inflammatory response that is associated with an inability to eliminate a pathogen and with the resultant tissue damage that leads to disease.

TRANSMISSION TO NEW HOSTS

As part of the pathogenic process, most microbes are shed from the host, often in a form infectious for susceptible individuals. However, the rate of transmissibility may not necessarily be high, even if the disease is severe in the infected individual, as these traits are not linked. Most pathogens exit via the same route by which they entered: respiratory pathogens by aerosols from sneezing or coughing or through salivary spread, gastrointestinal pathogens by fecal-oral spread, sexually transmitted diseases by venereal spread, and vector-borne organisms by either direct contact with the vector through a blood meal or indirect contact with organisms shed into environmental sources such as water. Microbial factors that specifically promote transmission are not well characterized. Respiratory shedding is facilitated by overproduction of mucous secretions, with consequently enhanced sneezing and coughing. Diarrheal toxins such as cholera toxin, *E. coli* heat-labile toxins, and *Shigella* toxins probably facilitate fecal-oral spread of microbial cells in the high volumes of diarrheal fluid produced during infection. The ability to produce phenotypic variants that resist hostile environmental factors (e.g., the highly resistant cysts of *E. histolytica* shed in feces) represents another mechanism of pathogenesis relevant to transmission. Blood parasites such as *Plasmodium* spp. change phenotype after ingestion by a mosquito—a prerequisite for the continued transmission of this pathogen. Venereally transmitted pathogens may undergo phenotypic variation due to the production of specific factors to facilitate transmission, but shedding of these pathogens into the environment does not result in the formation of infectious foci.

In summary, the molecular mechanisms used by pathogens to colonize, invade, infect, and disrupt the host are numerous and diverse. Each phase of the infectious process involves a variety of microbial and host factors interacting in a manner that can result in disease. Recognition of the coordinated genetic regulation of virulence factor elaboration when organisms move from their natural environment into the mammalian host emphasizes the complex nature of the host-parasite interaction. Fortunately, the need for diverse factors in successful infection and disease implies that a variety of therapeutic strategies may be developed to interrupt this process and thereby prevent and treat microbial infections.

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121 LABORATORY DIAGNOSIS OF INFECTIOUS DISEASES

The laboratory diagnosis of infection requires the demonstration, either direct or indirect, of viral, bacterial, fungal, or parasitic agents in tissues, fluids, or excreta of the host. Clinical microbiology laboratories are responsible for processing these specimens and also for determining the antibiotic susceptibility of bacterial pathogens. Traditionally, detection of pathogenic agents has relied largely on either the microscopic visualization of pathogens in clinical material or the growth of microorganisms in the laboratory. Identification is generally based on phenotypic characteristics, such as fermentation profiles for bacteria, cytopathic effects in tissue culture for viral agents, and microscopic morphology for fungi and parasites. These techniques are reliable but are often time-consuming. Increasingly, the use of nucleic acid probes is becoming a standard detection and/or identification method in the clinical microbiology laboratory, gradually replacing phenotypic characterization and microscopic visualization methods.

DETECTION METHODS

Reappraisal of the methods employed in the clinical microbiology laboratory has led to the development of strategies for detection of pathogenic agents through nonvisual biologic signal detection systems. Much of this methodology is based on either computerization of detection systems with relatively inexpensive but sophisticated computers or the use of nucleic acid probes directed at specific DNA or RNA targets. This chapter discusses both the methods that are currently available and those that are being developed.

BIOLOGIC SIGNALS A *biologic signal* is a material that can be reproducibly differentiated from other substances present in the same physical environment. Key issues in the use of a biologic (or electronic) signal are distinguishing it from background noise and translating it into meaningful information. Examples of biologic signals applicable to clinical microbiology include structural components of bacteria, fungi, and viruses; specific antigens; metabolic end products; unique DNA or RNA base sequences; enzymes; toxins or other proteins; and surface polysaccharides.

DETECTION SYSTEMS A detector is used to sense a signal and to discriminate between the signal and background noise. Detection systems range from the trained eyes of a technologist assessing morphologic variations to sensitive electronic instruments, such as gas-liquid chromatographs coupled to computer systems for signal analysis. The sensitivity with which signals can be detected varies widely. It is essential to use a detection system that discerns small amounts of signal even when biologic background noise is present—i.e., that is both sensitive and specific. Common detection systems include immunofluorescence; chemiluminescence for DNA/RNA probes; flame ionization detection of short- or long-chain fatty acids; and detection of substrate utilization or end-product formation as color changes, of enzyme activity as a change in light absorbance, of turbidity changes, of cytopathic effects in cell lines, and of particle agglutination.

AMPLIFICATION Amplification enhances the sensitivity with which weak signals can be detected. The most common microbiologic amplification technique is growth of a single bacterium into a discrete colony on an agar plate or into a suspension containing many identical organisms. The advantage of growth as an amplification method is that it requires only an appropriate growth medium; the disadvantage is the amount of time required for amplification. More rapid specific amplification of biologic signals can be achieved with techniques such as polymerase (ligase) chain reactions (PCRs, for DNA/RNA), enzyme immunoassays (EIAs, for antigens and antibodies), electronic amplification (for gas-liquid chromatography assays), antibody capture methods (for concentration and/or separation), and selective filtration or centrifugation. Although a variety of methods are available for the amplification and detection of biologic signals in research, thorough testing is required before they are validated as diagnostic assays.

DIRECT DETECTION

MICROSCOPY The field of microbiology has been defined largely by the development and use of the microscope. The examination of specimens by microscopic methods rapidly provides useful diagnostic information. Staining techniques permit organisms to be seen more clearly.

The simplest method for microscopic evaluation is the wet mount, which is used, for example, to examine cerebrospinal fluid (CSF) for the presence of *Cryptococcus neoformans*, with India ink as a background against which to visualize large-capsuled yeast cells. Wet mounts with dark-field illumination are also used to detect spirochetes from genital lesions and to reveal *Borrelia* or *Leptospira* in blood. Skin scrapings and hair samples can be examined with use of either 10% KOH wet-mount preparations or the calcofluor white method and ultraviolet illumination to detect fungal elements as fluorescing structures. Staining of wet mounts—for example, with lactophenol cotton blue stain for fungal elements—is often used for morphologic identification. These techniques enhance signal detection and decrease the background, making it easier to identify specific fungal structures.

STAINING **Gram's Stain** Without staining, bacteria are difficult to see at the magnifications (400 to 1000×) used for their detection. Although simple one-step stains can be used, differential stains are more common. Gram's stain differentiates between organisms with thick peptidoglycan cell walls (gram-positive) and those with outer membranes that can be dissolved with alcohol or acetone (gram-negative).

Gram's stain is particularly useful for examining sputum for polymorphonuclear leukocytes (PMNs) and bacteria. Sputum specimens with 25 or more PMNs and fewer than 10 epithelial cells per low-power field often provide clinically useful information. However, the presence in "sputum" samples of more than 10 epithelial cells per low-power field and of multiple bacterial types suggests contamination with oral microflora. Despite the difficulty of discriminating between normal microflora and pathogens, Gram's stain may prove useful for specimens from areas with a large resident microflora if a useful biologic marker (signal) is available. Gram's staining of vaginal swab specimens can be used to detect epithelial cells covered with gram-positive bacteria in the absence of lactobacilli and the presence of gram-negative rods—a scenario regarded as a sign of bacterial vaginosis. Similarly, examination of stained stool specimens for leukocytes is useful as a screening procedure before testing for *Clostridium difficile* toxin or other enteric pathogens.

The examination of CSF and joint, pleural, or peritoneal fluid with Gram's stain is useful for determining whether bacteria and/or PMNs are present. The sensitivity is such that $>10^4$ bacteria per milliliter should be detected. Centrifugation is often performed before staining to concentrate specimens thought to contain low numbers of organisms. The pellet is examined after staining. This simple method is particularly useful for examination of CSF for bacteria and white blood cells or of sputum for acid-fast bacilli (AFB).

Acid-Fast Stain The acid-fast stain identifies organisms that retain carbol fuchsin dye after acid/organic solvent disruption (e.g., *Mycobacterium* spp.). Modifications of this procedure allow the differentiation of *Actinomyces* from *Nocardia* or other weakly acid-fast organisms. The acid-fast stain is applied to sputum, other fluids, and tissue samples when AFB (e.g., *Mycobacterium* spp.) are suspected. The identification of the pink/red AFB against the blue background of the counterstain requires a trained eye, since few AFB may be detected in an entire smear, even when the specimen has been concentrated by centrifugation. An alternative method is the auramine-rhodamine combination fluorescent dye technique.

Fluorochrome Stains Fluorochrome stains, such as acridine orange, are used to identify white blood cells, yeasts, and bacteria in body fluids. Other specialized stains, such as Dappe's stain, may be used for the detection of *Mycoplasma* in cell cultures. Capsular, flagellar, and spore stains are used for identification or demonstration of characteristic structures.

Immunofluorescent Stains The direct immunofluorescent antibody technique uses antibody coupled to a fluorescing compound, such as fluorescein, and directed at a specific antigenic target to visualize organisms or subcellular structures. When samples are examined under appropriate conditions, the fluorescing compound absorbs ultraviolet light and reemits light at a higher (visible) wavelength detectable by the human eye. In the indirect immunofluorescent antibody technique, an unlabeled (target) antibody binds a specific antigen. The specimen is then stained with fluorescein-labeled polyclonal antibody directed at the target antibody. Because each unlabeled target antibody attached to the appropriate antigen has multiple sites for attachment of the second antibody, the visual signal can be intensified (i.e., amplified). This form of staining is called *indirect* because a two-antibody system is used to generate the signal for detection of the antigen. Both direct and indirect methods detect viral inclusions (e.g., cytomegalovirus and herpes simplex virus) within cultured cells as well as many difficult-to-grow bacterial agents (e.g., *Legionella pneumophila*) directly in clinical specimens.

MACROSCOPIC ANTIGEN DETECTION Latex agglutination assays and EIAs are rapid and inexpensive methods for identifying organisms, extracellular toxins, and viral agents by means of protein and polysaccharide antigens. Such assays may be performed directly on clinical samples or after growth of organisms on agar plates or in viral cell cultures. The biologic signal in each case is the antigen to be detected. Monoclonal or polyclonal antibodies coupled to a reporter (such as latex particles or an enzyme) are used for detection of antibody-antigen binding reactions.

Techniques such as direct agglutination of bacterial cells with specific antibody are simple but relatively insensitive, while latex agglutination and EIAs are more sensitive. Some cell-associated antigens, such as capsular polysaccharides and lipopolysaccharides, can be detected by agglutination of a suspension of bacterial cells when antibody is added; this method is useful for typing of the somatic antigens of *Shigella* and *Salmonella*. In systems such as EIAs, which employ antibodies coupled to an enzyme, an antigen-antibody reaction results in the conversion of a colorless substrate to a colored product. Because the coupling of an enzyme to the antibody can amplify a weak biologic signal, the sensitivity of such assays is often high. In each instance, the basis for antigen detection is antigen-antibody binding, with the detection system changed to accommodate the biologic signal. Most such assays provide information as to whether antigen is present but do not quantify the antigen. EIAs are also useful for detecting bacterial toxins—e.g., *C. difficile* toxins A and B in stool.

DETECTION OF PATHOGENIC AGENTS BY CULTURE

SPECIMEN COLLECTION AND TRANSPORT To culture bacterial, mycotic, or viral pathogens, an appropriate sample must be placed into the proper medium for growth (amplification). The success of efforts to identify a specific pathogen often depends on the collection and transport process coupled to a laboratory-processing algorithm suitable for the specific sample/agent. In some instances, it is better for specimens to be plated at the time of collection rather than first being transported to the laboratory (e.g., urethral swabs being cultured for *Neisseria gonorrhoeae* or sputum specimens for pneumococci). In general, the more rapidly a specimen is plated onto appropriate media, the better the chance for isolating bacterial pathogens. Appendix B lists procedures for collection and transport of common specimens. Because there are many pathogen-specific paradigms in these procedures, it is important to seek advice from the microbiology laboratory when in doubt about a particular situation.

ISOLATION OF BACTERIAL PATHOGENS Isolation of a suspect pathogen(s) from clinical material relies on the use of artificial media that support bacterial growth in vitro. Such media are composed of agar, which is not metabolized by bacteria; nutrients to support the growth of the species of interest; and sometimes substances to inhibit the growth of other bacteria. Broth is employed for growth (amplification) of organisms from specimens with few bacteria, such as peritoneal dialysis fluid, CSF, or samples in which anaerobes or other fastidious organisms may be present. The general use of liquid media for all specimens is not worthwhile.

Two basic strategies are used to isolate pathogenic bacteria. The first is to employ enriched media that support the growth of any bacteria that may be present in a sample such as blood or CSF, which contain no bacteria under normal conditions. Broths that allow the growth of small numbers of organisms may be subcultured to solid media when growth is detected. The second strategy is to isolate (amplify) specific bacterial species from stool, genital tract secretions, or sputum—sites that contain many bacteria under normal conditions. Antimicrobial agents or other inhibitory substances are incorporated into the agar medium to inhibit growth of all but the bacteria of interest. After incubation, organisms that grow on such media are further characterized to determine whether they are pathogens. Selection for organisms that may be pathogens from the normal microflora shortens the time required for diagnosis (Fig. 121-1).

ISOLATION OF VIRAL AGENTS (See also Chap. 180) Pathogenic viral agents often are cultured when the presence of serum antibody is not a criterion for active infection or when an increase in serum antibody may not be detected during infection. The biologic signal—virus—is amplified to a detectable level. Although a number of techniques are available, an essential element is a monolayer of cultured mammalian cells sensitive to infection with the suspected virus. These cells serve as the amplification system by allowing the proliferation of viral particles. Virus may be detected by direct observation of the cultured cells for cytopathic effects or by immunofluorescent detection of viral antigens following incubation. Culture methods are particularly useful for detection of rapidly propagated agents, such as cytomegalovirus or herpes simplex virus.

AUTOMATION OF MICROBIAL DETECTION IN BLOOD

The detection of microbial pathogens in blood is difficult because the number of organisms present in the sample is often low and the organisms' integrity and ability to replicate may be damaged by humoral defense mechanisms or antimicrobial agents. Over the years, systems that rely on the detection of CO_2 produced by bacteria and yeasts in blood culture medium have allowed the automation of the detection procedure. The most common systems involve either the insertion of a sampling device into each culture bottle at periodic intervals, with drawing off of the head-space gas for analysis by an infrared monitor or the use of reflectance optics, with a light-emitting diode and photodiode employed to detect a color change in a CO_2-sensitive indicator built into the bottom of the culture bottle. These systems measure CO_2 concentration as indicative of microbial growth. Sophisticated algorithms are used to evaluate the rate at which CO_2 is being produced and then to determine whether the rate of change is consistent with microbial growth. Such methods are no more sensitive than the human eye in detecting a positive culture; however, because the bottles in an automated system are monitored more frequently, a positive culture is often detected more rapidly than by manual techniques, and important information, including the result of Gram's stain and preliminary susceptibility assays, can be obtained sooner. One advantage of reflectance optic systems is that the bottles are scanned continuously in a noninvasive monitoring procedure, and thus the likelihood of laboratory contamination is decreased.

Automated systems also have been applied to the detection of microbial growth from specimens other than blood, such as peritoneal and other normally sterile fluids. *Mycobacterium* spp. can be detected in certain automated systems if appropriate liquid media are used for culture.

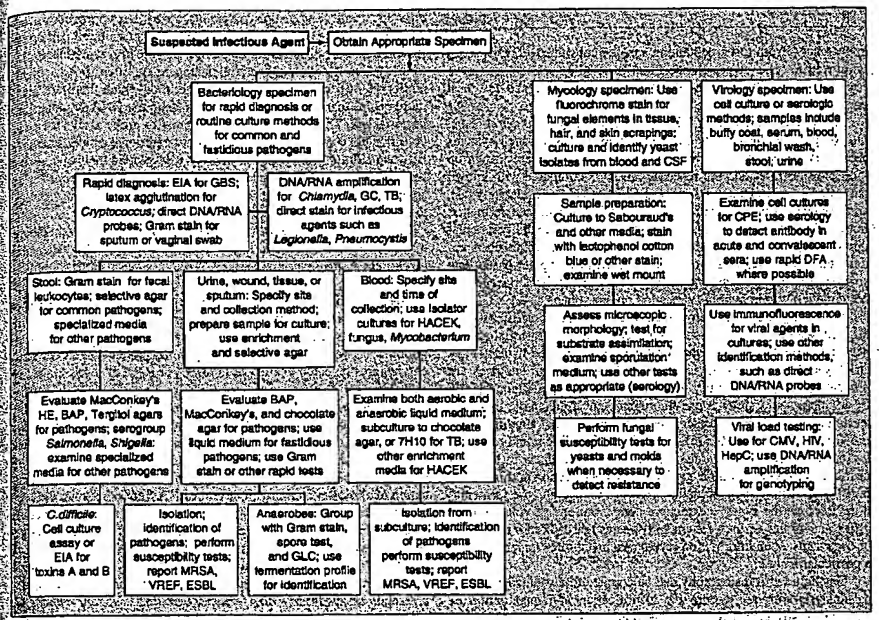

FIGURE 121-1 Common specimen-processing algorithms used in clinical microbiology laboratories. Abbreviations: BAP, blood agar plate; CMV, cytomegalovirus; CPE, cytopathic effects; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; ESBL, extended-spectrum β-lactamase; GBS, group B *Streptococcus*; GC, *Neisseria gonorrhoeae*; GLC, gas-liquid chromatography; HACEK, *Haemophilus aphrophilus/parainfluenzae/paraphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*; HE, Hektoen enteric medium; HepC, hepatitis C virus; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*; TB, *Mycobacterium tuberculosis*; VREF, vancomycin-resistant *Enterococcus faecium*.

DETECTION OF PATHOGENIC AGENTS BY SEROLOGIC METHODS

Measurement of serum antibody provides an indirect marker for past or current infection with a specific viral agent or other pathogens, including *Brucella, Legionella, Rickettsia,* and *Helicobacter pylori*. The biologic signal is usually either IgM or IgG antibody directed at surface-expressed antigen(s). The detection systems include those used for bacterial antigens (agglutination reactions, immunofluorescence, and EIA) and unique systems such as hemolysis inhibition and complement fixation. Serologic methods generally fall into two categories: those that determine protective antibody levels and those that measure changing antibody titers during infection. Determination of an antibody response as a measure of current immunity is important in the case of viral agents for which there are vaccines, such as rubella virus or varicella-zoster virus; assays for this purpose normally use one or two dilutions of serum for a qualitative determination of protective antibody levels. Quantitative serologic assays to detect increases in antibody titers most often employ paired serum samples obtained 10 to 14 days apart (i.e., acute- and convalescent-phase samples). Since the incubation period before symptoms are noted may be long enough for an antibody response to occur, the demonstration of acute-phase antibody alone is often insufficient to establish the diagnosis of active infection as opposed to past exposure. In such circumstances, IgM may be useful as a measure of an early, acute-phase antibody response. A fourfold increase in total antibody titer or in EIA activity between the acute- and convalescent-phase samples is also regarded as evidence for active infection.

For certain viral agents, such as Epstein-Barr virus, the antibodies produced may be directed at different antigens during different phases of the infection. For this reason, most laboratories test for antibody directed at both viral capsid antigens and antigens associated with recently infected host cells to determine the stage of infection.

IDENTIFICATION METHODS

Once bacteria are isolated, traditional methods of phenotypic characterization are often used to identify specific isolates. An organism's phenotypic characteristics include traits that are readily detectable after growth on agar media (colony size, color, hemolytic reactions, odor), use of specific substrates and carbon sources (such as carbohydrates), formation of specific end products during growth, and microscopic

appearance. Broth tubes containing specific substrates are commonly employed for phenotypic characterization. While such methods have been used since the time of Pasteur, their simplicity and low cost continue to make them appealing today.

CLASSIC PHENOTYPING Automated systems allow rapid phenotypic identification of bacterial pathogens. Most such systems are based on biotyping techniques, in which isolates are grown on multiple substrates and the reaction pattern is compared with known patterns for various bacterial species. This procedure is relatively fast, and commercially available systems include miniaturized fermentation, coding to simplify recording of results, and probability calculations for the most likely pathogens. If the biotyping approach is automated and the reading process is coupled to computer-based data analysis, rapidly growing organisms, such as Enterobacteriaceae, can be identified within hours of detection on agar plates.

Several systems use preformed enzymes for even speedier identification (within 2 to 3 h). Such systems do not rely on bacterial growth per se to determine whether a substrate has been used or not. They employ a heavy inoculum in which specific bacterial enzymes are present in sufficient quantity to convert substrate to product rapidly. In addition, some systems use fluorogenic substrate/end-product detection methods to increase sensitivity (through signal amplification).

GAS-LIQUID CHROMATOGRAPHY Gas-liquid chromatography is often used to detect metabolic end products of bacterial fermentations. One common application is identification of short-chain fatty acids produced by obligate anaerobes during glucose fermentation. Because the types and relative concentrations of volatile acids differ among the various genera and species that make up this group of organisms, such information serves as a metabolic "fingerprint" for a particular isolate.

Gas-liquid chromatography can be coupled to a sophisticated signal-analysis software system for identification and quantitation of long-chain fatty acids (LCFAs) in the outer membranes and cell walls of bacteria and fungi. For any given species, the types and relative concentrations of LCFAs are distinctive enough to allow identification of even closely related species. An organism may be identified definitively within a few hours after detection of growth on appropriate media. LCFA analysis is one of the most advanced procedures currently available for phenotypic characterization.

NUCLEIC ACID PROBES Techniques for the detection and quantitation of specific DNA and RNA base sequences in clinical specimens have become powerful tools for the diagnosis of bacterial, viral, parasitic, and fungal infections. The basic strategy is to detect a relatively short sequence of bases specific for a particular pathogen on single-stranded DNA or RNA by hybridization of a complementary sequence of bases (probe) coupled to a "reporter" system that serves as the signal for detection. Detection of an organism by nucleic acid probes offers a decided advantage over culture methods for difficult-to-grow organisms. Current technology encompasses a wide array of methods for amplification and signal detection, some of which have been approved by the U.S. Food and Drug Administration (FDA) for clinical diagnosis.

Use of nucleic acid probes generally involves lysis of intact cells and denaturation of the DNA or RNA to render it single-stranded. The probe may be hybridized to the target sequence in a solution or on a solid support, depending on the system employed. In situ hybridization of a probe to a target is also possible and allows the use of probes with agents present in tissue specimens. Once the probe has been hybridized to the target (biologic signal), a variety of strategies may be employed to amplify and/or quantify the target-probe complex (Fig. 121-2).

Probes for Direct Detection of Pathogens in Clinical Specimens Nucleic acid probes are available commercially for direct detection of various bacterial and parasitic pathogens, including *L. pneumophila*, *Chlamydia trachomatis*, *N. gonorrhoeae*, group A *Streptococcus*, *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Giardia lamblia*. In addition, probes for direct detection of human papillomavirus, *Candida* spp., and *Trichomonas vaginalis* have been approved. An assortment of probes for confirming the identity of cultured pathogens such as *Mycobacterium* and *Salmonella* spp., are also available. Probes for the direct detection of bacterial pathogens are often aimed at highly conserved 16S ribosomal RNA sequences, of which there are many more copies than there are of any single genomic DNA sequence in a bacterial cell. The sensitivity and specificity of probe assays for direct detection are comparable to those of more traditional assays, including EIA and culture. Many laboratories have developed their own probes for pathogens; however, unless a method-validation protocol for diagnostic testing has been performed, the use of such probes is restricted to research by federal law in the United States.

Nucleic Acid Probe Target-Amplification Strategies In theory a single target nucleic acid sequence can be amplified to detectable levels. There are several strategies for target and/or probe amplification, including PCR, ligase chain reaction, strand displacement amplification, and self-sustaining sequence replication. In each case, a target sequence or hybridized probe is amplified exponentially to obtain sufficient signal for detection, usually by the attachment of chemiluminescent reporter groups to the amplified product. The PCR strategy requires repeated heating of the DNA or RNA to separate the two complementary strands of the double helix, hybridization of a primer sequence to the appropriate target sequence, target amplification using the PCR for complementary strand extension, and signal detection via a labeled probe. The sensitivity of such assays is far greater than that of traditional assay methods such as culture. However, the care with which the assays are performed is important, because cross-contamination of clinical material with DNA or RNA from other sources (even at low levels) can cause false-positive results. An alternative method employs transcription-mediated amplification, in which an RNA target sequence is converted to DNA, which is then exponentially transcribed into RNA target. The advantage of this method is that only a single heating/annealing step is required for amplification. At present, amplification assays for *Mycobacterium tuberculosis*, *N. gonorrhoeae*, *C. trachomatis*, and *M. hominis* are on the market. Again, many laboratories have used commercially available *taq* polymerase, probe sequences, and reagents to develop "in-house" assays for diagnostic use. Issues related to quality control, interpretation of results, sample processing, and regulatory requirements have slowed the commercial development of diagnostic assay kits.

Signal Amplification Strategies Alternative systems for signal amplification have great appeal, particularly for quantitative determination of the amount of target present in a given specimen. With the advent of newer therapeutic regimens for HIV-associated disease, cytomegalovirus infection, and hepatitis C virus infection, the response to therapy has been monitored by determining both genotype and "viral load" at various times after treatment initiation. Target amplification (PCR, transcription-mediated amplification) is difficult to control in a manner that allows accurate determination of the original target (genome) concentration. In other systems, probes attached to complementary target sequences are amplified by the attachment of a second probe and an amplification multimer to the original probe. In one such system, branched-chain DNA (bDNA)-based amplification, bDNA is attached to a site different from the target-binding sequence of the original probe. Chemiluminescent-labeled oligonucleotides can then bind to multiple repeating sequences on the bDNA. The amplified bDNA signal is detected by chemiluminescence. Alternatively, a DNA probe may be attached to an RNA target and the resulting DNA/RNA hybrid captured on a solid support by antibody specific for DNA/RNA hybrids (concentration/amplification) and detected by chemiluminescent-labeled antibody specific for DNA/RNA hybrids. Both methods can be used to determine the approximate number of target copies (virus) in the starting material. The advantage of these systems over PCR is that only a single heating/annealing step is required to hybridize the target-binding probe to the target sequence for amplification.

Application of Nucleic Acid Probe Technology Nucleic acid probe technology is being used to identify difficult-to-grow or noncultivable bacterial pathogens, such as *Mycobacterium*, *Legionella*, *Ehrlichia*, *Rickettsia*, *Babesia*, *Borrelia*, and *Tropheryma whippelii*. Amplification methods are also being used to detect chronic viral infections, such as herpes simplex encephalitis, cytomegalovirus infection, and hepatitis C. The monitoring of therapy with quantitative viral-load testing is a significant new application of nucleic acid technology. Further applications will likely include the replacement of culture for identification of many pathogens with solid-state DNA/RNA chip technology, in which thousands of unique nucleic acid sequences can be detected on a single computer chip. Probe technology also has the potential to detect viral pathogens faster than is possible with current culture techniques. However, if laboratories are to take full advantage of probe technology, the cost of reagents and assay automation must be competitive with the cost of existing methodology. At present, the detection of agents such as *C. trachomatis* or *N. gonorrhoeae* by probe technology is more expensive for most laboratories than detection by traditional culture or EIA. Moreover, because automated processing equipment is just beginning to find its way into the laboratory for these assays, nucleic acid amplification methods are both more labor-intensive and more expensive than other detection systems. In the absence of clear documentation of clinical utility, many laboratories continue to wait for FDA approval of commercially available DNA/RNA probe assays rather than validating in-house assays.

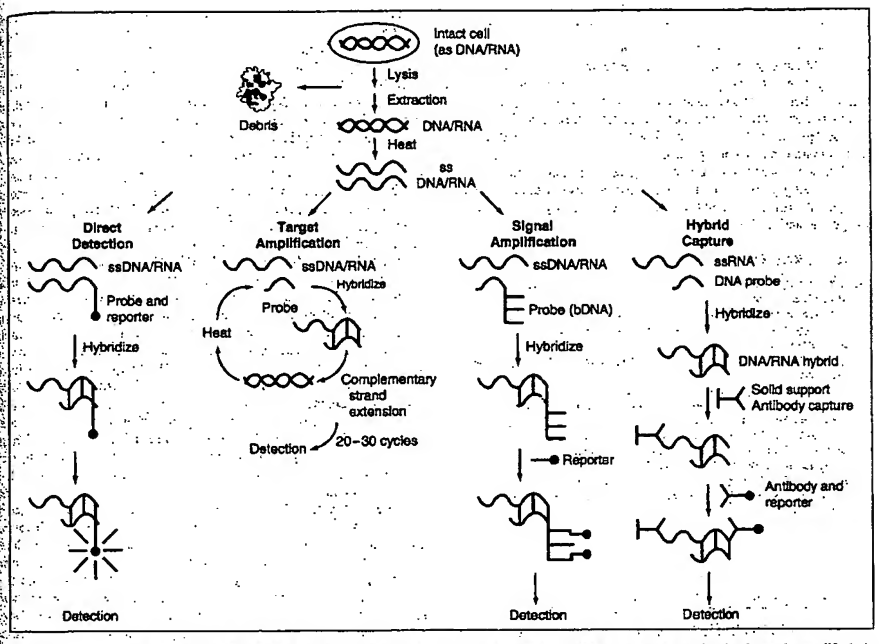

FIGURE 121-2 Strategies for amplification and/or detection of a target-probe complex. DNA or RNA extracted from microorganisms is heated to create single-stranded (ss) DNA/RNA containing appropriate target sequences. These target sequences may be hybridized directly (direct detection) with probes attached to reporter molecules; they may be amplified by repetitive cycles of complementary strand extension (polymerase chain reaction) before attachment of a reporter probe; or the original target-probe signal may be amplified via hybridization with an additional probe containing multiple copies of a secondary reporter target sequence (branched-chain DNA, or bDNA). DNA/RNA hybrids can also be "captured" on a solid support (hybrid capture), with antibody directed at the DNA/RNA hybrids used to concentrate them and a second antibody coupled to a reporter molecule attached to the captured hybrid.

SUSCEPTIBILITY TESTING A principal responsibility of the clinical microbiology laboratory is to determine which antimicrobial agents inhibit a specific bacterial isolate. Such testing is used to screen for infection control problems, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, or extended-spectrum β-lactamase-producing organisms. Two approaches are useful. The first is a qualitative assessment of susceptibility, with responses categorized as susceptible, resistant, or intermediate. This approach can involve either the placement of paper disks containing antibiotics on an agar surface inoculated with the bacterial strain to be tested (Kirby-Bauer or disk/agar diffusion method), with measurement of the zones of growth inhibition following incubation, or the use of broth tubes containing a set concentration of antibiotic (breakpoint method). These methods have been carefully calibrated against quantitative methods and clinical experience with each antibiotic, and zones of inhibition and breakpoints have been calculated on a species-by-species basis.

The second approach is to inoculate the test strain of bacteria into a series of broth tubes (or agar plates) with increasing concentrations of antibiotic. The lowest concentration of antibiotic that inhibits microbial growth in this test system is known as the *minimum inhibitory concentration* (MIC). If tubes in which no growth occurs are subcultured, the minimum concentration of antibiotic required to kill the starting inoculum can also be determined (*minimum bactericidal concentration*, or MBC). Quantitative susceptibility testing by the microbroth dilution technique, a miniaturized version of the broth-dilution technique using microwell plates, lends itself to automation and is commonly used in larger clinical laboratories.

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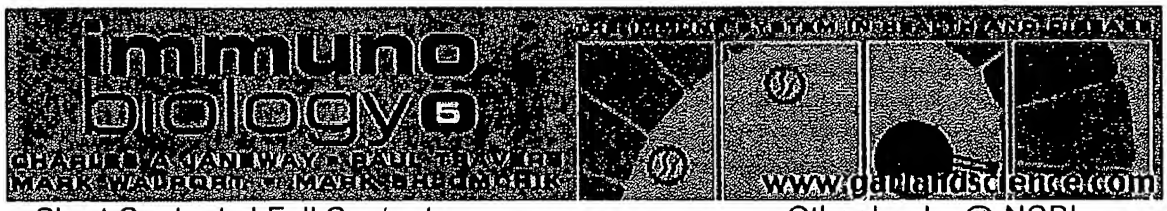

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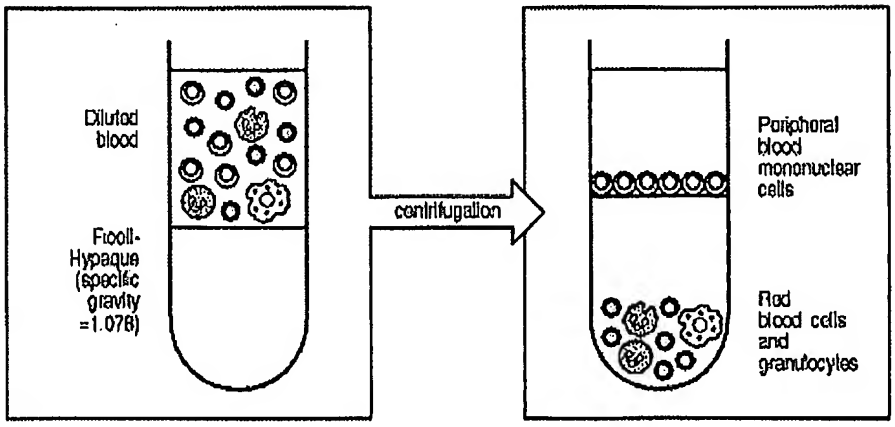

Figure A.23. Peripheral blood mononuclear cells can be isolated from whole blood by Ficoll-Hypaque™ centrifugation. Diluted anticoagulated blood (left panel) is layered over Ficoll-Hypaque™ and centrifuged. Red blood cells and polymorphonuclear leukocytes or granulocytes are more dense and centrifuge through the Ficoll-Hypaque™, while mononuclear cells consisting of lymphocytes together with some monocytes band over it and can be recovered at the interface (right panel).

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Consequences of different diagnostic 'gold standards' in test accuracy research: Carpal Tunnel Syndrome as an example

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Test accuracy studies assume the existence of a well-defined illness definition and clear-cut diagnostic gold standards or reference standards. However, in clinical reality illness definitions may be vague or a mere description of a set of manifestations, mostly clinical signs and symptoms. This can lead to disagreements among experts about the correct classification of an illness and the adequate reference standard. Using data from a diagnostic accuracy study in carpal tunnel syndrome, we explored the impact of different definitions on the estimated test accuracy and found that estimated test performance characteristics varied considerably depending on the chosen reference standard. In situations without a clear-cut illness definition, randomized controlled trials may be preferable to test accuracy studies for the evaluation of a novel test. These studies do not determine the diagnostic accuracy, but the clinical impact of a novel test on patient management and outcome.

Keywords Sensitivity and specificity, ROC curve, reference standards, carpal tunnel syndrome, ultrasonography

The notion of a diagnostic gold standard or reference standard pertains to the best available method for establishing the presence or absence of a condition of interest,[1] i.e. the independent and correct classification of what is meant to be the illness.[2] The traditional concept of a reference standard depends on a high level of biological understanding of the target condition and its causal underlying mechanisms. Typically, a morphological verification such as histopathology or angiography, is used to establish a 'definite diagnosis'. This definite diagnosis is assumed to be a reasonably reliable proxy measure of the true presence or absence of the condition of interest.

In conventional diagnostic accuracy studies, the usefulness of a novel test for the inclusion or exclusion of a specific condition will be determined by comparing the results of the test with the definite diagnosis ascertained by the reference standard. However, in clinical reality the biological understanding of conditions is frequently unclear. Illness definitions are vague or a mere description of a set of manifestations. In fields such as psychiatry and rheumatology, clinicians frequently use 'syndromal diagnoses' consisting of a characteristic pattern of signs and symptoms,[3] while the biological understanding of the condition, of its causes, and its manifestations is incomplete and there is controversy about the manifestations that have to be combined to ensure accurate representation of the condition. In other situations, the biological understanding of the condition may be comprehensive, but the measurement of signs or symptoms is inaccurate.

Two extreme conceptualizations of the reference standard may implicitly or explicitly be used in such circumstances. One extreme ignores potential controversies and assumes a well-defined illness, which is objectively and reproducibly represented by the outcome of one or several laboratory tests. The other extreme ignores potentially useful biological measures and focuses exclusively on patient outcomes or on the need for an intervention. While these two outlooks aim at describing the same issue, they may create a schism when evaluating a diagnostic test. Below, we will explore this in a clinical example of an accuracy study previously published by our group in the field of rheumatology[4] and discuss the potential implications for clinical research into conditions without a clear-cut reference standard by which to establish a diagnosis.

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Clinical example

Carpal Tunnel Syndrome (CTS) is an important cause of functional impairment and pain of the hand, which presumably results from a compression of the median nerve at the wrist. Unfortunately, there is no universally accepted reference standard to establish the diagnosis. In our experience, two different approaches towards CTS classification are used. Neurologists traditionally establish the definite diagnosis based more on the outcome of nerve conduction studies than on the patients' signs and symptoms. In contrast, hand surgeons appear to give considerably more importance to the patients' signs and symptoms, the severity of complaints and the likely need for and success of a surgical intervention than to nerve conduction studies when establishing the definite diagnosis. In our accuracy study,[1] we relied on current practice and pre-specified the neurologists' definite diagnosis as the reference standard. Here, we determine the impact of using either of the two 'reference standards' on the estimated test accuracy of sonography in patients with suspected CTS.

Methods and results

Details of methods are reported elsewhere.[1] We assessed 77 patients for eligibility, excluded 3 because of traumatic wrist lesions, and enrolled 74 referred to the outpatient clinic of the Department of Hand Surgery at the University Hospital Berne, Switzerland, between January and December 2002.

Patients included in the study had a mean age of 51 years and 48 were females (65%). The flow of patients through the various stages of the study is described elsewhere.[1] Essentially, 101 wrists from 71 patients were included in the analysis.

Standardized nerve conduction studies were performed by one of several neurologists, who were unaware of the results of the sonographic examination. The sonographic evaluations were performed by a rheumatologist experienced in musculoskeletal sonography, who was unaware of the results of the nerve conduction studies and of the patients' signs and symptoms. He performed transverse imaging of the median nerve for the area ranging from the distal forearm to the outlet of the carpal tunnel and measured the largest cross-sectional area of the median nerve in square millimetres. We used this measure as a single diagnostic indicator, assuming that an increase in cross-sectional areas is associated with an increasing likelihood of disease or disease severity.

Table 1 presents a comparison of definite diagnoses according to neurologists' and hand surgeons' judgements. Overall agreement was 86%. One out of 23 wrists classified as normal by the neurologists was considered as CTS by the hand surgeons (4%). This wrist had normal nerve conduction studies. Conversely, 13 out of 78 wrists classified as CTS by the neurologists were considered normal by the hand surgeons (17%); all 13 wrists had pathological nerve conduction studies. The resulting kappa for the agreement between the two illness definitions was 0.67 [95% confidence interval (CI) 0.48–0.85].

Table 1 2 × 2 contingency table comparing reference standard classifications according to neurologists and hand surgeons

	Hand surgeons' judgements		
	CTS present	CTS absent	Total
Neurologists' judgements			
CTS present	65	13	78
CTS absent	1	22	23
Total	66	35	101

For both reference standards, we fitted a receiver operating characteristic (ROC) curve for diagnosis of CTS by sonography, using a maximum likelihood logistic regression model based on robust standard errors, which allowed for the correlation of characteristics of wrists within patients and compared the area under the ROC curve. Figure 1 shows the fitted ROC curves using either the neurologists' judgements (top) or the hand surgeons' judgements (bottom) as the reference standard. The area under the ROC curve for ultrasound was 0.89 based on neurologists' judgements (95% CI 0.82–0.96) and 0.77 based on hand surgeons' judgements (95% CI 0.68–0.87). The difference between the two areas under the ROC curve was 0.12 (95% CI 0.0–0.23).

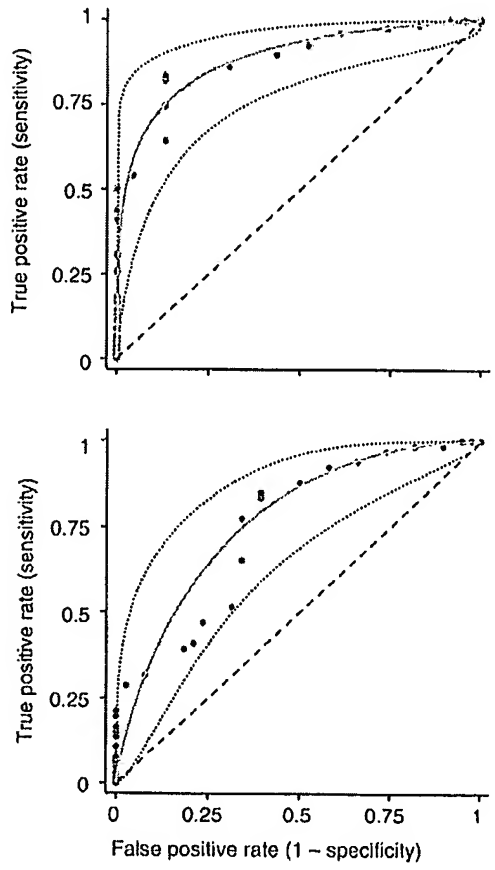

Figure 1 Fitted ROC curves (solid curve) for diagnosis of CTS by sonography with 95% confidence interval (dotted curves), considering the neurologists' definite diagnosis (top) or the hand surgeons' definite diagnosis as the reference standard (bottom). The broken diagonal line represents a hypothetical ROC curve of a test that yields no diagnostic information

Discussion

Even though the agreement between the two employed illness definitions was substantial (a kappa of 0.67), the estimated test performance of ultrasound varied considerably depending on the definition used as the reference standard. The diagnostic accuracy of sonography in patients with suspected CTS was good to excellent according to one reference standard but only moderate according to the other.

The lack of consensus on an illness definition may impede a valid evaluation of diagnostic technology in test accuracy studies. Considering that the final purpose of any novel test is to improve patient management and outcome, the traditional paradigm of test accuracy studies will only be useful if a reference standard is chosen that either has a strong association with patient outcome or a direct relationship with patient management. In our accuracy study[4] we argued, for example, that the neurologists' definite diagnosis directly pertains to clinical decision making and patient management.

Ultimately, the use of a diagnostic test and its potential therapeutic consequences can be considered as two consecutive steps of the same management strategy. Analogous to traditional research into therapeutic interventions, randomized trials may be designed to compare different strategies. In such trials, patients will be randomly allocated to a management strategy that includes the use of a novel test under evaluation, or to a strategy that uses standard tests only. Ascertained outcomes may relate to parameters of patient management (e.g. length of hospital stay), to patient outcome (e.g. pain), or to the total cost of management per patient.[5] If an unanimously accepted reference standard is lacking, as is the case in CTS, such randomized controlled trials may be more appropriate than test accuracy studies to determine the usefulness of a novel diagnostic test.

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